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# CANCER OF THE BREAST

## THE SCOPE OF IRRADIATION*

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### RATIONALE

Although energetic radiation can penetrate to any region in the human body, it has serious quantitative limitations. The delivery to the whole of the potentially malignant area of a dose of radiation sufficient to destroy the tumour, and yet within the tolerance of the patient's organism, requires a nice consideration of numerous technical factors. The first of these is the *radio-sensitivity of the tumour*. This is measured by the smallest dose of radiation which will permanently eradicate the neoplasm in all, or most, of the cases treated. Since this quantity encroaches on the upper limits of tolerance of normal tissues, it is important to consider all the factors which may affect its magnitude.

The concept of a minimum lethal dose for a tumour does not represent a static quantity. The process of necrobiosis of irradiated cells is one that requires time, involves the exchange of certain unidentified metabolites, and a subtle change in the relation of a cell to the surrounding tissues. The classical radiobiological experiments of Goldfeder (1942) have shown that the curative action of radiation is not directly due to destruction of the tumour. The curative dose in the animal body is of the order of *one tenth* of that required to destroy the same tumour in tissue culture. This difference is associated with an acquired immunity on the part of the connective tissues towards irradiated tumour. Since clinical doses, too, are far smaller than the lethal dose for tumours in tissue culture, the direct destructive effect of radiation can be discounted in practice.

This immune reaction is dependent on the integrity of the supporting stroma, and the *interaction between irradiated tumour and its stroma* is one of the most important factors to be considered in the curability of human cancer. Histological examination of human tumours after optimal doses of radiation reveals a brisk 'stromal reaction' on the part of the vascular and connective tissues with an active exudation of phagocytic cells. Interference with this reaction by ischaemia, endarteritis, fibrosis, or anything causing local anoxia, *protects* the tumour from the effects of radiation, so that tumours growing in avascular tissues are likely to be radio-resistant.

It is, therefore, not surprising that the same tumour in different locations can differ in its radio-sensitivity. It is a common experience that one fails to eradicate by radiation a cancer surrounded by adipose tissue in the depths of the breast, while a satellite nodule from the same tumour growing in the subcutaneous tissue or in bone is easily permanently healed. It is probable, too, that the lymph node metastases from a mammary carcinoma are materially more sensitive than the primary growth.

The foregoing facts should be applied in the rational therapy of breast cancer. The malignant cells in the affected area can be considered in three distinct biological categories:

1. Cells *in situ* in the breast;
2. Cells in transit in lymphatic vessels;
3. Cells in the regional nodes.

Each of these categories reacts independently to irradiation and to surgery.

*Radiation*, it has been noted:—

i. Cannot, with the ordinarily applied techniques, eradicate cancer *in situ* in the breast, probably on account of the avascular stroma;

ii. Should, with adequate dosage, render cells in transit incapable of establishing themselves in tissues with an adequate stroma, i.e. in lymph nodes, viscera or bones;

iii. Can, in adequate dosage, eradicate breast cancer in the lymph nodes.

*Surgery*, on the other hand, it is well-known from experience:—

i. Can remove cancer localized to the breast;

ii. Does not remove cells in the lymph spaces, but on the contrary, tends to disperse them;

iii. Cannot eradicate cancer in lymph nodes, and dissection of involved nodes is rarely successful.

It follows that only by a rational combination of the

* The first part of this article was published in the *Journal* of 15 April 1950, pp. 276-280.

two procedures can tumour in all three categories be eradicated. It is not proposed here to discuss the appropriate surgical procedures. The radical mastectomy operation, its indications, its technique and its limitations are well known. McWhirter has made a strong plea for local mastectomy combined with intensive irradiation. With the perfection of our radiation techniques, with precise knowledge of the MLD for mammary cancer, and with the optimal exploitation of the time factor, it seems logical that the McWhirter procedure will become accepted as the treatment of choice. It is also impossible at this stage to make a choice between pre-operative and post-operative radiation, although recent statistics tend slightly to favour the former.

## DOSAGE

No clear-cut definition of the curative dose for breast cancer is available in the literature. Temporary regression of an irradiated mammary cancer is easily obtained, but permanent eradication of the growth often appears to require dosage levels not easily attainable in practice. A careful comparison of results in cases treated pre-operatively with different doses, and assessed by histological analysis of the surgical specimen, is given by Lenz (1946). In these cases treatment was delivered at 200 KVP, and the over-all treatment time was in the region of 60 days. When the total dose was less than 5500 r, cancer persisted in all cases and microscopic evidence of viable cancer cells was still obtained in a proportion of cases receiving 7000 r. Many other workers, employing essentially similar techniques, have found all but the highest doses inadequate in eradicating this tumour. This suggests that breast carcinoma *in situ* is extremely radio-resistant.

In certain instances, however, permanent cures had been obtained with much lower dosage. In contrast to the results of Lenz and his colleagues of the American school, relatively good results have been obtained in Britain (McWhirter, 1949) with smaller doses delivered in *a shorter time interval*. McWhirter claims that 3750 r in 18 days is biologically more effective than 7000 r in 60 days. Since the time-factor seems of paramount importance in influencing the radio-sensitivity of mammary carcinoma, it is necessary to review the influence of treatment time on the response of tissues to radiation.

## THE TIME FACTOR

The majority of the reactions to radiation in the animal organism show a marked dependence on the over-all time of the irradiation. In general the longer the time of treatment the greater the total dose required to elicit a given effect. This implies a certain degree of recovery on the part of the tissues from the effects of radiation. The recovery rate varies with different tissues, and the author (Cohen, 1949) demonstrated how they could be determined and compared. In the case of epidermoid cancer the recovery rate is less than that of normal skin, so that the protracted fractionated regime (Coutard method) is uniformly successful in the treatment of carcinomas of squamous cell origin. However, there is no reason why this should also apply to non-epidermoid tissues, so it was decided to investigate the effects of the time factor on the response of mammary cancer to given doses of radiation.

For this purpose 25 cases of proved mammary cancer, recurrent after mastectomy, were selected. They consisted mainly of accessible cutaneous recurrences, and axillary or supraclavicular metastases localized to a single node, treated with accurately determined dosage before 1948, and followed through 1950. Cases were classified as 'recurrent' or 'local cure' according to their behaviour during the three years' follow-up. The results are summarised in Fig. 1. The co-ordinates give the total dose in 'r' and the over-all time in 'days' respectively, using logarithmic scales after the author's (1949) method. Each circle represents a locally cured case; each cross a recurrence within the treated field. The lettering refers to the published data discussed previously, which, in general, agree with out experimental points.

It is immediately apparent that a single line can be drawn separating the cures from the recurrences. This represents the true minimum lethal dose for the tumour. For comparison a dotted line showing the skin tolerance dose for a 20 cm. field is included. It will be noticed that the margin of safety diminishes as the over-all time is increased. Contrary to the situation with epidermoid tumours, therefore, *there is no advantage in protracting treatment in mammary cancer.*

For this reason we have seen fit to shorten our routine course for breast cases to a two-week, and recently to a one-week technique. Although several cases treated in this way have developed metastases, we have never seen a recurrence within the treated zone. Although it is too soon finally to evaluate the results of the procedure or to decide whether the incidence of metastases is lower than with other techniques, immediate results can be considered entirely satisfactory.

## TECHNIQUE

It has been found satisfactory to apply the same technique irrespective of the extent of the disease or whether the treatment is to be pre-operative, post-operative, or merely palliative. High voltage rontgen radiation generated at 250 KVP with 1 mm. Cu and 1 mm. Al filtration is directed through five fields, as illustrated in Fig. 2. Fields I and II are directed tangentially to the chest wall (in pre-operative treatments this would include the breast) and cover the area between the sternal field and the posterior axillary line. With the patient supine, they are angled at 45° downwards and upwards respectively, so that the two fields are directly opposed and the intervening tissue homogeneously irradiated. Fields III and IV are directed through the axilla and supraclavicular regions, anteriorly and posteriorly, so that the block of tissue sandwiched between them is homogeneously irradiated. Field V is only 5 cm. wide, is centred over the sternum and directed through the mediastinum so that the internal mammary nodes, which lie about 2 cm. below the skin, receive 90% of the surface dose.

With fields of suitable size (between 15 and 20 cm. in length), therefore, it is physically possible to achieve homogeneous dosage to the whole of the first echelon in the advance of the neoplasm. In the case of exceedingly obese patients, however, the penetration obtainable with ordinary deep-therapy equipment is not sufficient to achieve uniform dosage on account of the large separation between the paired fields. Although this can be partially compensated with an additional field on the chest wall, it is impossible to avoid getting a lower dose at the apex of the axilla. For this

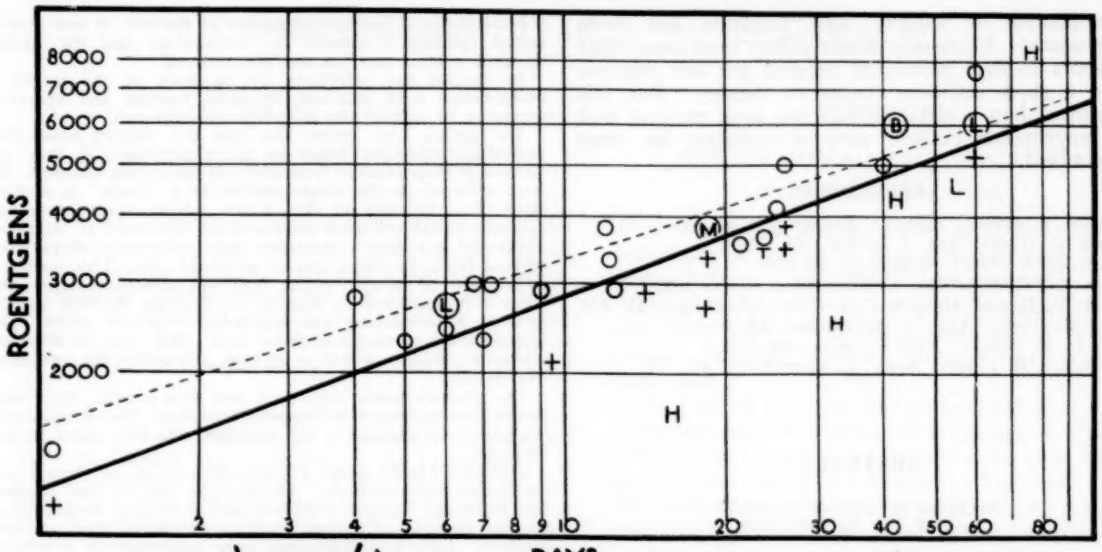


FIG.1

*Fig. 1.* Twenty-five cases of mammary cancer treated in 1948. Circles represent local cures; crosses local recurrence. Lettering refers to authors quoted in the References.

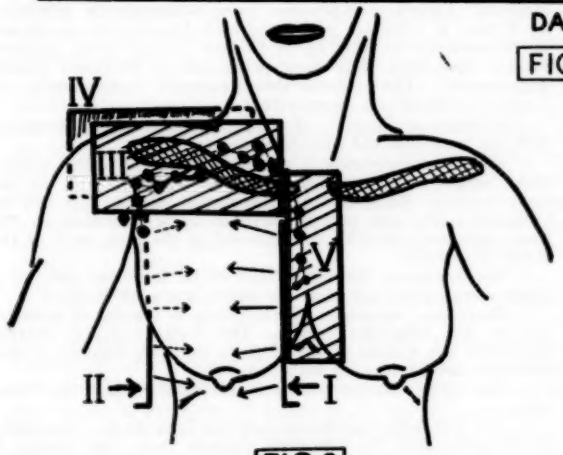


FIG.2

*Fig. 2.* Arrangement of fields for the treatment of a carcinoma of the right breast.

I. Medial tangential field } directly opposed.
II. Lateral tangential field }
III. Anterior axilla and supraclavicular } opposed.
IV. Posterior axilla and supraclavicular }
V. Sternal field.

reason a very radical clearance of the axilla is indicated in all excessively obese women.

The optimal dose for a two-week course (Fig. 1) should be not less than 3500 r. We have found 350 r daily to each portal, for 10 treatments, excluding a two-day interval at the week-end, a satisfactory routine. This will give a minimum tissue dose of 3500 r in 12 days, and a maximum of 4000 r to the skin if exit doses are considered.

A moderate degree of radiation sickness affects most patients during this procedure, probably due to the somewhat large daily dose. Haemopoietic changes have not been marked, and considering the short duration of the treatment, blood counts are probably unnecessary. The skin reaction appears only after the conclusion of the treatment, and patients are spared the discomfort, unavoidable with longer routines, of being treated in the presence of a painful erythema. The reaction goes on to a moist desquamation in all cases, and heals spontaneously in a few weeks requiring only simple dressings.

### INTERVAL BETWEEN SURGERY AND RADIATION

In the post-operative routine, therapy can be commenced 10 days or more after the operation, as soon as the incision has healed. In the case of pre-operative irradiation, our shortened regime has yielded an unexpected advantage. *It is possible to perform the mastectomy on the day following the last treatment.* In this way the operation is completed and the wound heals normally during the latent period before the radiation reaction appears. Convalescence is not complicated in any way by this procedure. Compared to the longer routine, which may entail a delay of six weeks or more before the skin is sufficiently healthy for operative purposes, this is an immense saving in time.

The pre-operative method is particularly advantageous in technically inoperable cases. Intensive irradiation followed by local excision has given satisfactory remissions even in very advanced stages of the disease. Adequate pre-operative irradiation apparently eliminates the danger of dissemination by cutting through malignant tissue. In the case of distant metastases, too, gratifying symptomatic relief can be obtained with radiation, a single dose of 1500 r to the lesion generally sufficing to produce local healing.

### SUMMARY

It has been pointed out that few of the standard techniques hitherto published solve the fundamental problems of breast cancer. The necessity for a rational

combination of surgery and radiation has been emphasized. Mammary cancer differs from most other tumours in that protracted regimes are less effective than a short intensive course of therapy. For this reason a short routine method has been evolved, and the appropriate curative dose of radiation has been determined.

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## ABSTRACT

ARCHIVES OF OTOLARYNGOLOGY*
Vol. 49, No. 4, April 1949.

This volume is devoted almost entirely to the work on the ear conducted in the Department of Surgery, University of the Witwatersrand, and is therefore of particular South African interest. The first two papers were presented by Dr. Popper to the Section on Laryngology, Otology and Rhinology at the Ninety-seventh Annual Session of the American Medical Association, Chicago, 24 June 1948.

In presenting a hydrodynamic hypothesis of hearing the author has been influenced by deductions from cases in which hearing has been restored by operation, both for otosclerosis and for deafness caused by chronic ear infections.

For over four centuries no reasonable explanation has been given why the organ of balance and the organ of hearing should be so closely connected. Popper offers the following explanation. The organs of balance are the semi-circular canals and sacs. They are stimluated by minute differences of fluid pressure of the endolymph contained within them. This fluid pressure is of a continuous character. The stimulus required by the organ of hearing is also in the nature of infinitesimal pressure differences. The latter, however, are interrupted and reciprocating. Such interruptions may be from 16 to 30,000 times per second, which covers the extremes of the perceptible human sound spectrum. These impulses are transmitted to the cochlea via the perilymph. The perilymph must, therefore, be disposed mechanically in the system where it is able to move back and forth.

The two galleries of the cochlea communicate with each other and their ends are mobile—the oval and the round windows respectively. This is an ideal hydrodynamic system. Should one of these ends lose its mobility, such as fixation of the stapes in otosclerosis, the hydrodynamic system is destroyed and impaired hearing ensues. Otosclerosis is not deafness but a break-down of the hydrodynamics of the ear. A new mobile sealed opening is created by fenestration and the hydrodynamic system and hearing are restored.

In chronic ear infections the mobility of the stapes is embarrassed with resultant impaired hearing and operative measures to restore this mobility are indicated.

The author also points out that the ossicles have their individual functions, which is to be expected, as they are derived phylogenetically from different embryonic elements. To have referred to the three ossicles as a 'chain' is nothing short of a calamity in that it has misled investigators and delayed logical operative measures for the relief of deafness. The stapes is mainly a protective organ of immense importance derived from the entire second or hyoid arch. The incus has a function of counter-acting stapedial muscular action and when it is destroyed by disease the resulting deafness can be relieved by abolishing the unopposed stapedial action. The hydrodynamic conception opens up a long vista in this new operative otology, which is carried out under the operating microscope.

*The Transtympanic Approach and Fenestration* deals with the detailed technique of Popper's operation. The technicalities are mainly of interest to the otologist who has access to this literature.

Professor Lund's paper *Popper's Operation for Otosclerosis* covers the same territory. He explains that he has adopted this technique because it offered such a striking simplification for the operation for otosclerosis as compared with previous methods. Lund's modifications were independently published by Popper in a further paper and have found wide acceptance in Scandinavia as well as in Europe. (Over three hundred Popper operations have been performed in Professor Lund's department.) The considerable technical conveniences of Popper's method are summarized.

*Advantages of Popper's Method*: The advantages, compared with the trans-mastoid operation, are as follows:

1. The entire operation is performed under excellent survey, with 'square-on' presentation of the posterior wall of the bony meatus. Thus the tympanomeatal plastic flap can be loosened easily and rapidly, without being preceded by the time-consuming thinning and removal of the bony wall of the posterior meatus.

2. The tympanic membrane has to be loosened only to a slight extent (even less than the extent given by Popper).

3. There is a 'square-on' presentation of the site of fenestration in the vestibular cupola. The facial canal is sharply defined in the middle of the field, so that any injuring of this structure can be avoided with certainty.

4. The entire mastoid process is left intact—which also saves time.

5. The tympanic membrane does not have to be 'stretched' as recommended by Lempert, because here the fistula is situated so far anteriorly that it is covered easily simply by laying the tympanomeatal flap down; moreover, the flap even extends out on the medial wall of the antrum.

6. It is unnecessary here to remove the head of the malleus (this is done in Lempert's method) because the plastic flap is sufficiently large to make the aforementioned 'stretching' superfluous.

7. The operative trauma is considerably smaller than with the procedure given by Lempert.

Dr. Ewertsen's article is an analysis of hearing improvement obtained by Popper's method in Copenhagen.

Dr. Rasmussen analyses the vestibular functions of 79 patients before and after the Popper operation; 27 of these patients had vestibular disturbances before the operation and the symptoms were considerably reduced in 14 of the cases after operation.

Dr. Riskaer presents a brief survey the calcium, inorganic phosphate, cholesterol and protein fraction contents of the blood serum of patients with otosclerosis. The divergent results are pointed out.

Dr. Svend Selso presents an investigation on the conditions of the external audiotory meatus and the tympanic membrane in pateints with otosclerosis, and comes to the conclusion that the external auditory meatus and the tympanic membrane present no characteristics that may contribute to differentiate otosclerosis from other forms of impaired hearing.

*Contents: Hydrodynamics and Hearing: I. The Operative Relief of Otosclerotic and Nonotosclerotic Deafness and Its Relationship to a Hydrodynamic Hypothesis of Hearing; a Suggested Explanation for (a) the Intimate Association of the Organs of Balance and the Organ of Hearing and for (b) the Function of the Incus. Otto Popper, M.B., Ch.B., F.R.C.S. (Edin.).
Transtympanic Approach and Fenestration: II. The Current Technic. Otto Popper, M.B., Ch.B., F.R.C.S. (Edin.).
Acoustic, Vestibular and Other Problems Concerning Otosclerosis and its Surgical Treatment According to Popper's Method. Robert Lund, M.D.: Harald Ewertsen, M.D., Helmer Rasmussen, M.D., Niels Riskaer, M.D., and Svend Selso, Copenhagen, Denmark.
I. Popper's Operation for Otosclerosis. Robert Lund, M.D.
II. Acoustic Function Before and After Operation for Otosclerosis. Harald Ewertsen, M.D.
III. Vestibular Function Prior to and Following Operation for Otosclerosis, Helmer Rasmussen, M.D.
IV. Biochemical Conditions in Patients with Otosclerosis, Niels Riskaer, M.D.
V. Conditions of the External Auditory Meatus and the Tympanic Membrane in Patients with Otosclerosis, Svend Selso.

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## VAN DIE REDAKSIE

### DIE BIOLOGIESE AKTIWITEITSEENHEID

### SY STATUS EN OMVANG

Die begrip, biologiese eenheid, het ontstaan uit die behoefte om die aktiwiteit te meet van biologiese stowwe soos bv. serums, vitamiene, hormone en lewervernietigende middels waarvan die skeikundige samestelling nie presies bekend was nie of wat van heterogene aard was sodat daar geen konstante verhouding tussen gewig en aktiwiteit bepaal kon word nie.

Die begrip is die eerste teen die end van die vorige eeu deur Ehrlich toegepas op die standaardisering van die anti-toksien vir witseerkeel en sedertdien is standaardeenhede vir baie biologiese stowwe bepaal. Die taak om internasionaal erkende aktiwiteitseenhede vas te stel deur die kritiese vergelyking van resultate in die laboratoriums van verskillende lande verkry, is eers deur die Permanente Kommissie insake Biologiese Normalisering van die Volkebond se Gesondheidsorganisasie verrig. Vandag word hierdie werk deur die Deskundige Komitee oor Biologiese Normalisering van die Wêreld-gesondheidsorganisasie gedoen. Gedurende die afgelope 25 jaar is vir meer as 30 stowwe op hierdie wyse eenhede omskryf en standaarde vasgestel, met inbegrip van serums—onder andere teen witseerkeel en tetanus—tuberkulien, digitalis, ouabain, insulien, die arsenobensols, sekere hormone, sekere vitamiene, heparin, penisillin en streptomisien.

'n Kritiese studie van die begrip biologiese eenhede en van sekere probleme wat uit die gebruik daarvan voortspruit, word in die *Bulletin of the World Health Organization*[1] verstrek deur dr. A. A. Miles, Direkteur van die Departement van Biologiese Standaarde van die *National Institute of Medical Research*, Londen, en lid van die Wêreld-gesondheidsorganisasie se Deskundige Komitee oor Biologiese Normalisering. Nadat hy die stadiums in herinnering geroep het wat gelei het tot die vasstelling van die eerste eenheid, dié van antitoksien van witseerkeel, wat 'n klassieke voorbeeld geword het, ondersoek die skrywer die waarde van die ‚dier-eenheid', 'n woord wat dikwels en verkeerd gebruik word vir die uitdrukking ‚reeks van kleinste dosisse wat vir 'n bepaalde dier afdoende is'. Dit is in werklikheid onmoontlik (deur die reaksies van lewende organismes op die inspuiting van aktiewe stowwe te vergelyk) om resultate te kry wat konstant genoeg is en wat eng genoeg begrens is vir die vasstelling van internasionaal erkende eenhede. Die gebruik van die woord ‚dier-eenheid', wat dikwels selfs verkort word tot ‚eenheid', sonder om aan te dui watter diersoort gebruik word, moet laat vaar word.

Na oorweging van die voorwaardes waaraan voldoen moet word deur die begrip eenheid indien laasgenoemde geldig moet wees, skenk dr. Miles vervolgens oorweging aan die kwessie van heterogene standaarde en die laaste

1. *Bull. World Hlth. Org.* (1949): **2**, 205.

## EDITORIAL

### THE BIOLOGICAL UNIT OF ACTIVITY

### ITS STATUS AND SCOPE

The concept of a biological unit arose from the need to measure the activity of biological substances, such as sera, vitamins, hormones and antibiotics, whose chemical constitution was not precisely known or which were heterogeneous in nature so that no constant relation between weight and activity could be established.

The concept was first applied by Ehrlich at the end of the last century to the standardization of diphtheria antitoxin, and since then standard units have been set up for many biological substances. The task of fixing internationally recognized units of activity by the critical comparison of results obtained in laboratories in various countries was first carried out by the Permanent Commission on Biological Standardization of the League of Nations Health Organization. To-day this work is being performed by the Expert Committee on Biological Standardization of the World Health Organization. During the last 25 years, units have been defined and standards established in this way for more than 30 substances, including sera—antidiphtheria and antitetanus among others—tuberculin, digitalis, ouabain, insulin, the arsenobenzenes, certain hormones, certain vitamins, heparin, penicillin and streptomycin.

A critical study of the concept of biological units and of certain problems at present arising in their use is presented by Dr. A. A. Miles, Director of the Department of Biological Standards of the National Institute for Medical Research, London, and a member of the WHO Expert Committee on Biological Standardization, in the Bulletin of the World Health Organization.[1] After recalling the stages which led to the setting-up of the first unit, that for diphtheria antitoxin, now a classical example, the author examines the value of the 'animal-unit', a term frequently and incorrectly used instead of the expression 'the range of minimal effective doses in a given animal'. It is, in fact, impossible (by comparing the reactions of living organisms to the injection of active substances) to obtain results sufficiently constant and lying between narrow enough limits to serve as a basis for setting up internationally recognized units. The use of the term 'animal-units', which is even frequently abridged to 'unit' without indicating the species of animal used, should be abandoned.

After considering the conditions which should be satisfied by the concept of a unit, if the latter is to be valid, Dr. Miles next considers the question of heterogeneous standards, and the last part of his article

1. Bull. World Hlth. Org. (1949): **2**, 205.

deel van sy artikel word gewy aan 'n ondersoek van die probleme wat betrokke is by die afskaffing van die eenheidaanduiding wanneer biologiese stowwe, oorspronklik van onsuiwere en heterogene aard, deur die skeikundige en fisikus finaal gesuiwer en gekenskets is. Dit is die geval met vitamien C en vitamien $B_1$ waarvan die skeikundige samestelling nou bekend is en waarvan die kragtigheidsbepaling maklik is sonder dat biologiese toetse nodig is.

By ander stowwe is daar egter 'n grensstadium waar die standaard nie meer nodig is nie, in die sin dat dit in teorie moontlik is om biologiese aktiwiteit uit die resultate van 'n skeikundige ondersoek te voorspel, maar waar die standaard behou word omdat biologiese kragtigheidsbepaling goedkoper en makliker is. In sulke gevalle kan daar 'n mate van voordeel in steek om die kragtigheid, nie in eenhede nie, maar in gewigekwivalente aan te dui. Dié gewigekwivalent-metode word in die V.S.A. aangewend vir die bereiding van streptomisien terwyl die eenheidaanduiding in die Verenigde Koninkryk daarenteen behou word. Die skrywer bespreek hierdie voorbeeld en verduidelik waarom die eenheidaanduiding in die Verenigde Koninkryk verkies word. Na sy mening kan die weergawe van aktiwiteit deur die gewigekwivalent-metode slegs van besliste waarde wees indien die standaardpreparaat suiwer en homogeen is en indien daar aangeneem kan word dat alle daaropvolgende standaarde wat bedoel is om die hoofstandaard te vervang, dieselfde graad van suiwerheid sal hê.

Wat streptomisien betref, is die probleem van die relatiewe waardes van die eenheid en die gewigekwikalent nie slegs van bloot praktiese belang nie. 'n Kwessie van beginsel wat belangrike gevolge mag hê is daarby betrokke. 'n Nasionale of internasionale standaard is 'n noodsaaklike deel van amptelike omskrywings in farmakopeias en regeringsregulasies wat òf wet is òf gebruik word as 'n grondslag vir regsgedinge of handelstransaksies. Dit is dus belangrik om te verseker dat die amptelike eenheid presies omskryf is ten einde enige verwarring of misverstand te voorkom. Vir die organiese skeikunde byvoorbeeld is ‚streptomisien' 'n basis met 'n struktuurformule wat ooreenkom met N-metiel-l-glukosaminido-streptosido-streptidine. Dit is nie die ‚streptomisien' van die farmakopeia nie, wat beteken ‚elkeen van die verskeie lewevernietigende middels wat deur die kweking *Streptomyces griseus* geproduseer word: d.w.s. dat die verskillende stowwe wat almal hierdie naam dra hoegenaamd nie eenders is nie en dat hulle, gewig teen gewig nie dieselfde uitwerking sal hê nie. Die begrip eenheid daarenteen verwys na die aktiwiteit van 'n standaardpreparaat en nie na 'n stof wat as suiwer veronderstel word nie.

Die belangrikheid van die probleme wat die voorbarige afskaffing van die eenheidstelsel vergesel, is dus duidelik. Sulke probleme sal ongetwyfeld dikwels in die toekoms ontstaan soos meer en meer stowwe met biologiese aktiwiteit eers skeikundig omskryf en dan sinteties vervaardig word. Volgens dr. Miles sal die eenheidaanduiding onnodig word slegs wanneer biologiese kragtigheidsbepaling nie meer nodig is vir die spesifisering van stowwe wat volgens roetine voorberei word nie en wanneer slegs skeikundige en fisiese toetse genoegsaam is om biologiese aktiwiteit te voorspel.

is devoted to a study of the problems involved in discarding the unit notation when biological substances, originally of a crude or heterogeneous nature, have been finally purified and characterized by the chemist and physicist. This is the case with vitamin C and vitamin $B_1$, whose chemical constitution is now known and which are easy to assay without the need for biological tests.

With other substances, however, there is a borderline stage where the standard is no longer necessary, in the sense that it is theoretically possible to predict biological activity from the results of a chemical examination, but where the standard is retained because biological assay is cheaper and easier. In such cases, there may be some advantage in designating potency not in units, but in weight-equivalents. This weight-equivalent method has been adopted in the U.S.A. for preparations of streptomycin, while in the United Kingdom, on the other hand, the unit notation for this substance is retained. The author discusses this example, explaining why in the United Kingdom the unit notation is preferred. In his opinion the expression of activity by the weight-equivalent method can be of real value only if the standard preparation is pure and homogeneous and if it can be assumed that all subsequent standards intended to replace the master standard will be of the same degree of purity.

As regards streptomycin, the problem of the relative values of the unit and the weight-equivalent is not only of purely practical interest. A question of principle, which may have important consequences, is involved. A national or international standard is an essential part of official definitions in pharmacopoeias and government regulations which are either law or are used as a basis for legal proceedings and commercial transactions. It is, therefore, important to make sure that the official unit is precisely defined so as to avoid any confusion or misunderstanding. For example, to the organic chemist, 'streptomycin' is a base with a structural formula corresponding to N-methyl-*l*-glucosaminido-streptosido-streptidine. This is not the 'streptomycin' of the pharmacopoeia which means 'each of several antibiotic substances produced by the growth of *Streptomyces griseus*': i.e. that the different substances all bearing this name are far from being identical and that, weight by weight, they will not have the same biological activity. The concept of a unit, on the other hand, refers to the activity of a standard preparation and not to a hypothecial pure substance.

The importance of the problems inherent in a premature discarding of the unit system is therefore evident. There can be no doubt that such problems will frequently arise in the future as more and more substances with biological activity are first chemically defined and then synthesized. According to Dr. Miles, unit notation will become superfluous only when biological assay ceases to be indispensable for the specification of materials prepared routinely and when chemical and physical tests alone are sufficient to predict biological activity.

# PROGRESS IN THE STUDY OF THE MODES OF ACTION OF THE HUMAN UTERUS DURING PREGNANCY AND LABOUR*

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AND
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## INTRODUCTION

Nowhere in the field of Obstetrics is there a lack of knowledge so restricting as that concerning the physiology of uterine action. This view is based on the belief that disordered action of the uterus is the origin of the vast majority of abnormalities encountered in labour. While the gross effects of variations in muscular activity are well known to the Obstetrician, it is entirely in retrospect that a hypothetical concept of the morphology and contractility of this great mass of smooth muscle has been formulated. We might inquire, for instance, as to whether our ideas of retraction are intelligible, or again how it happens that the firm uterus associated with the ligneous abdomen of severe, toxaemic, accidental haemorrhage so readily exhibits profound atony. Significant phenomena about which a modicum of information is required are the cause of onset of labour at term, and the fact that uterine contractions are intermittent and not continuous. Both mechanisms appear commonplace because they are seen regularly and are inherent in parturition, but they are very striking and defy satisfactory explanation. A sound knowledge of the physiology of the myometrial contractility and activity in its various forms would represent a significant advance in the diagnostic, prognostic, and above all therapeutic departments of human parturition.

Recourse to electro-physiology for these requirements is not an unimaginative pursuit of a vogue, but suggests itself as being a promising method of approach and the one which should be the first to be explored. Mechanical methods depending on the insertion of balloons into the uterine cavity have the disadvantage of artificial stimulation by the foreign body, and provide only gross effects closely comparable with manual palpation of the organ contracting intermittently. Much can be learned from the last method of observation, though only in a casual way; it is admitted that in a clinical sense we have learned much, but only sufficient to stimulate a desire to know something truly fundamental about the action of this highly developed muscular organ. How much is likely to emerge from the recording of uterine action potentials is one purpose of this paper: the second concerns the development of methods used by others and by ourselves.

## HISTORICAL

Mechanical records of uterine action were made by Schatz (1872), Heinricius (1889), Acconci (1891), Knaus (1929), Moir (1934), and Lackner (1937).

Electrical studies on smooth muscle date back to 1843 (Matteucci), Fuchs (1910) and Foà (1914) reporting results this century.

Uterine electrical phenomena were studied by recording action currents and potentials in such mammals as the guinea-pig, cat, and rat by Orbeli (1910), Blumenfeldt and Dahlmann (1914), Alvarez and Mahoney (1922), Funke (1922), Richter (1924), Hasama (1930), Vozza (1933), Rosenblueth *et al.* (1933), Bozler (1938, 1941).

Finally the human uterus was studied for the first time in 1910 by Theilhaber. Then followed Veit (1912), Bode (1931), Falk and Nahon (1935), Jacobson *et al.* (1939), Langman and Burr (1942).

The historical position may be summarised, with reference to uterine electrical phenomena, by stating that the string galvanometer or modification was used mainly and was sometimes accompanied by a simultaneous mechanical recording. In animals a potential of about 1 millivolt was obtained and a frequency of 10-15 cycles per second. The deflections were more or less proportional to the uterine contractions, but it is reported with surprise that sometimes there were deflections without a contraction. Bode (1931) seems to have been the first worker to attempt to record changes in electric potential from the human uterus during labour.

## RECENT DEVELOPMENTS

In 1944 the present authors considered whether work could not be undertaken in South Africa to further knowledge in this sphere from the more specifically obstetrical point of view. They were concerned to learn something of uterine behaviour in the actual stages of labour. The natural starting point was to use the methods developed by Hasama (1930) and Bozler (1938 and 1941), Accordingly some preliminary experiments were carried out using a string galvanometer and needle electrodes directly attached to the uterine wall of an animal. (Rabbits and Guinea-pigs were used.) It was soon realised that the problems of having apparatus set up and personnel ready to observe rabbit and guinea-pig uteri in actual labour were very great because of the difficulty of timing the onset of labour and the very short period of labour in these animals. Accordingly it was decided to switch to experiments on human uteri. In deciding what line of attack to use we were guided by the following considerations.

The methods so far used for study of the uterus can be divided into two general categories. In the first category fall those studies in which the observers sought to record physical movement by a change in volume of the uterus, or a change in curvature of the anterior wall of the abdomen. Here it has been recognised that the change of volume was of little value for it merely indicated that the uterus had contracted and gave a relative

*This paper was read at the Medical Congress held at Cape Town September 1949.

indication of the magnitude of the contraction, and palpation will give the first information and will partially give the second information. In the second category fall those methods where a search has been made for an electrical signal which would be an indication of uterine activity.

The classical example of an electrical signal accompanying a biological activity is the potential wave accompanying the transmission of a nervous impulse. Here the biological impulse is accompanied by an electrical potential wave, which passes along the nerve, and which can be recorded at different points along its path. The time interval in which this impulse passes any given point on the nerve is very short, so that the amplifying of the electrical signal produced can be easily accomplished by conventional electronic amplifiers sensitive to frequencies of 30 cycles a second and over. As a result a good many of the earlier studies of the electrical potentials from uterine muscle were made with such amplifiers, with the results indicated above; that variations in amplitude of fairly high frequency signals were observed from uterine muscle, but in general it was not found possible to correlate these variations of amplitude with the contraction waves responsible for parturition.

In studying voluntary muscle movement and the nervous action responsible for it, any given movement is completed in a matter of seconds and the amount of record (photographic paper or ink tracing) is not more than a few feet. On the other hand a single uterine contraction will take from two to five minutes and the whole action of the uterus (the expulsion of a foetus) may take hours. Here the recording paper used to note all the high frequency potential changes in that time will run into hundreds of feet and the human problem of handling the paper, let alone reducing the records to some form of order and pattern, is enormous. We were therefore in favour of electrical recording, and on the basis of the above discussion decided to look for a long period electrical signal which would need a short length of recording paper and to make no experimental arrangements which would prejudice the chance of obtaining a large number of observations on women patients with the minimum trouble to them and to the labour wards. This meant that there could be no thought of making electrical connections to the uterus itself. However, the history of the measurements of electrical impulses from the human heart, by means of connections to the arm or leg, showed that much might be achieved with electrodes fastened directly to the abdomen.

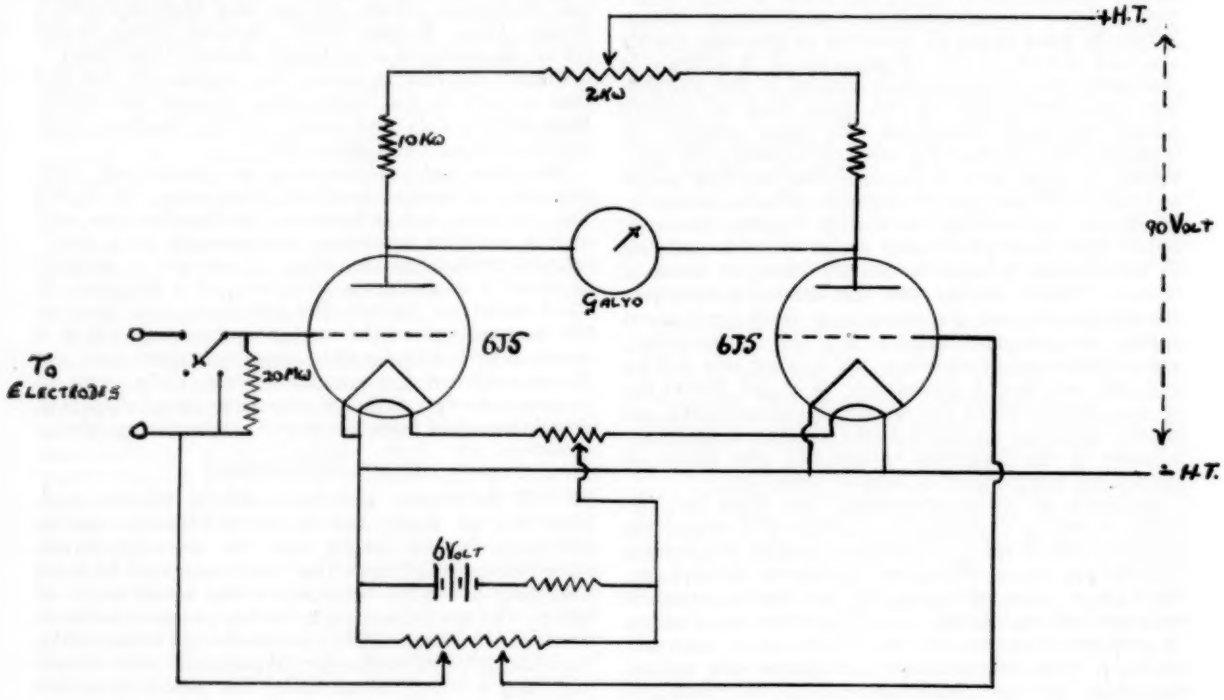


Fig. 1

We accordingly constructed in 1945 an apparatus as shown in Figure 1, which is actually a simplification of the Burr recording voltmeter. Two triode valves are connected to two resistances in wheatstone bridge fashion. The grid of the one valve is kept at a fixed potential while the two leads from the two uterine electrodes are connected, one to the filament and the other to the grid of the other valve. A galvanometer is connected between the two plates (anodes) of the two valves. A change of the uterine potential throws the

bridge out of balance and produces a deflection of the galvanometer. By means of this circuit, variations of the high tension battery potential or the filament battery potential can be balanced out so that the instrument shows no 'drift' in the recording over half an hour or longer. The recording has been done with a galvanometer made by the Cambridge Instrument Co. in which recording marks are made every quarter minute, and in which the galvanometer automatically switches itself from one pair of electrodes to another for alternate dots of the record. In this way one galvanometer was able to do the work of two which reduced expense for a preliminary study. It was found that as the action cycles of the uterus extend over a matter of several minutes quite a clear picture of potential changes could be obtained.

The electrodes which we finally settled upon, after trials of a number of types, were made from a block of ebonite about two inches long by one inch wide, with a hole bored right through the centre. This hole is lined with a ring of silver-plated brass which is in electrical connection with a terminal on the ebonite, to which the wire from the recording apparatus may be fastened. The electrode is held against the abdomen by a rubber band passing right round the body and then the hole is filled with electro-cardiograph jelly to make a semi-non-polarising electrode. It was customary to work with one of these electrodes making contact with the upper arm as an indifferent electrode, and to have one recording electrode over the fundus of the uterus and one electrode over the lower segment of the uterus. With this apparatus a series of studies was made during 1945 after which work was interrupted by the removal of one of the authors (E. C. H.) to Pretoria. In spite of this, work was continued at a slower pace and more intermittently, and is still in progress.

In 1946 Dill and Maiden published a paper in which they described measurements of potential patterns from abdominal electrodes on pregnant women, the recordings being made with either the electrocardiograph or the electro-encephalograph. They showed that there were no high frequency potential waves present and decided that the right line of development was to use recording apparatus designed to record very low frequency variations only. They indicated that they were going to continue on these lines. In 1947 two papers appeared describing methods of study along the line of measuring mechanical movement. The first concerns the Lorand Tocograph used by Murphy who has to his credit a number of publications since 1940 culminating in a monograph entitled 'Uterine Contractility in Pregnancy'. The instrument is essentially a mechanical recorder based on the rod and lever principle. The other report was by Reynolds (1947). A so-called 'Tokodynamometer' was used embodying a Statham strain-gauge. As in Murphy's instrument the signal is essentially a mechanical movement of the abdominal wall, which the strain-gauge records as a galvanometer deflection. Reynolds has so far reported on the instrument but not on observations with the instrument. In 1948 Dill and Maiden published again, and this time described measurements with a commercial Direct Current amplifier and an Esterline Angus recording milliammeter, so that their apparatus and ours had become fundamentally of the same nature. They do not make it clear for how long they made their studies on each case observed but, from the speed of movement of the recording paper which they mention, three inches per minute, it seems likely that each study did not last more than an hour.

## OBSERVATIONS

*Murphy* (1947) has made over 3,000 records, most of which were taken during pregnancy. He has made a very full analysis of these records from which the following three statements are selected.

*Pregnancy.* He describes a quiescent period, ending a the 20th week of pregnancy, which is characterised by an almost complete lack of contractions.

*Labour.* He states that 'the pattern of contraction during labour is peculiar to the individual', but 'the contraction pattern of early labour persists throughout the labour'.

*Drugs.* He notes the influence of Morphine in reducing the intermittent contractions of the uterus slightly but to a greater degree than the reduction of tone.

*Reynolds* (1947) has given a description of his instrument, but has so far not reported any observations made with it.

*Dill and Maiden* (1948) recorded potentials in 31 cases of which all that were in true labour had been treated with an analgesic including that by the caudal route in 14 cases. They report loss of electrical activity in these cases. In the light of this fact their conclusions may be summarised by extracting two of their four concluding remarks.

'Progressive labour is associated with over-all changes of potential of several millivolts of no definitely reduplicable pattern, path of conduction, or point of origin'.

'Contractions are associated in general with a higher standing voltage and possibly slightly less active than are the "between contractions" periods'.

*Halliday and Heyns.* Our records number only a little over 100, but it must be realised that a fair proportion of the labour tracings represent continuous recordings for more than five hours, there being two such periods of 9¾ and 10¼ hours respectively. The electrical response was studied during pregnancy in 22 cases and during labour in 68 cases. Of the latter 19 included third stages and postpartum periods.

Generally speaking, potentials varying between 5 and 150 mv. were observed in all these cases, and were accompanied by deflection waves when uterine activity was periodic. Positive potentials were almost the rule, but negative phases for which no explanation was obvious were obtained occasionally. Potentials beyond 160 millivolts which was the limit of the apparatus occurred rarely, but the tendency was for variations to occur around 50-60 mv. and not exceeding 80 mv. Other workers have not appreciated that these high uterine potentials occur. The usual pattern of potential variation consisted of a rise of potential at the beginning of a contraction followed by a fall at the end. These changes were of the order of a few millivolts though the standing potential might be 50 mv., but the shape of the

potential wave varied from individual to individual. As a rule the electrode placed over the fundus indicated a higher potential than that over the lower segment just above the symphysis pubis, the former also giving greater deflections. Where the lower segment is undergoing pronounced stretching, and particularly at the end of the second stage, the suprapubic electrode characteristically exhibits high potentials with large fluctuations. Unequivocal contractions appear invariably to give a deflection, but the amplitude is not necessarily proportional to the strength of the contraction. Variations in potential also occur in the absence of an appreciable contraction or of the sensation of pain.

Three striking effects are noteworthy:

i. Certain narcotics appear to prevent the galvanometer deflections and are associated with potentials lower than the average. Morphine and Hyoscine in combination produced this effect so powerfully that we began to reject for observation patients so narcotised. Morphine alone (three patients) did not act in this manner, nor did Pethedine (seven patients) appear to influence the electrical record.

ii. In 11 out of 22 pregnant women (27 to over 40 weeks) a remarkably high potential level occurred, positive in seven and negative in four. Deflections were unusual, but in a post-mature case the fundal voltage was of the order of 150 mv. The lower segment record was near to zero generally, but not always. This finding was unexpected, for in all these cases there were no appreciable contractions. This phenomenon was most obvious in post-maturity, but appeared to be present before 30 weeks' pregnancy more than between 30 and 40.

iii. The immediate postpartum period with its firmly contracted uterus characteristically gave a zero or very low potential indicating absence of strong muscular activity (see Fig. 2). It was thought at first that this was clear evidence of a lack of versatility of the electrical method of recording. However, this and other evidence are now believed by us to point to the probability that at the end of the third stage the uterus is in fact in a quiescent state which, after a period of uninterrupted stretching during pregnancy, represents rest rather than active contraction. Nineteen third stages were studied with our apparatus and two with the electro-encephalograph, the latter showing high frequency responses reaching 20 cycles per second at voltages of the order of 50 microvolts. Monophasic variations early in the third stage strongly suggest activity of certain layers of uterine muscle during separation of the placenta; moreover, it appears that the separation is effected some minutes after the birth of the child. In record J. (Mrs. S), for example, the uterus was relaxed for six minutes during which there were three waves of positive potential of five to eight millivolts from each of two electrodes. This was followed by visible tensing of the uterus with negligible potentials. After this there were pronounced diphasic responses up to 15 millivolts in each direction for five minutes and culminating in expulsion of the placenta. The evidence available appears to support the clinical impression that the placenta normally separates in seven minutes after the commencement of the third stage. Apparently separation may take place at the very end of the second stage during a slow forceps extraction with unhurried delivery of the shoulders.

## CONCLUSION

Experiment with the valve voltmeter indicates that the electrical responses obtained are the result of uterine activity, and cannot be produced by peristalsis or such muscular activity as occurs in the abdominal wall. It cannot be said with certainty that the voltages are derived directly from the uterus, but there can be little doubt that the action potentials are a fairly true reflection of the uterine activity which they accompany.

At present there is no advantage in attempting to record high frequency potential changes, and a long period electrical signal has proved its efficiency in the study of uterine behaviour. There are many aspects of contractility which must be observed during pregnancy as well as labour, during the exhibition of analgesic drugs, and particularly in the presence of inco-ordinate action of the uterus. When general behaviour patterns are revealed, more intensive study with other apparatus may be indicated for the elucidation of special points.

*Editor's Note.* It is regretted that Fig. 2 mentioned in the text and representing an electrical record of 80 minutes of a labour, could not be included on account of technical difficulties in connection with its reproduction.

# PROCEDURES IN THE CONTROL OF TUBERCULOSIS

## THE PRACTICAL APPROACH: 2. HOSPITALIZATION

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The cost of caring for the sick has been rising steadily over the last few years. This is seen particularly in the cost of hospital buildings. The average cost to-day of a hospital bed in South Africa is approximately £2,000. It is estimated that one bed per annual death is the minimum for the proper control of tuberculosis. Most countries suggest 2-3 beds per annual death and in some areas (U.S.A.) it is even considered that 10 beds per annual death are necessary.

In the Union of South Africa the actual number of deaths from tuberculosis reported for the year ending June 1949 was:

| *European* | *Native* | *Asiatic* | *Coloured* |
|---|---|---|---|
| 386 | 4706 | 388 | 2203 |

*Total:* 7,683

The notifications and deaths for 5 years were:

| | *Notifications* | *Deaths* | | |
|---|---|---|---|---|
| | | *European* | *Non-European* | *Total Deaths* |
| 1949 .. .. | 24,675 | 386 | 7,297 | 7,683 |
| 1948 .. .. | 22,668 | 452 | 6,755 | 7,207 |
| 1947 .. .. | 19,533 | 427 | 6,622 | 7,049 |
| 1946 .. .. | 19,773 | 463 | 6,565 | 7,028 |
| 1945 .. .. | 18,099 | 458 | 6,546 | 7,004 |
| *Average per year during first 5 years* .. | 20,949 | 437 | 6,757 | 7,194 |

The fact that vital statistics for non-Europeans are non-existent in rural areas forces one to estimate the real number of deaths—an estimate based on the following figures. We do not know the degree of accuracy of our estimates.

Population (Union) 1946:—

| | |
|---|---|
| European .. .. | 2,372,690 |
| Asiatic .. .. .. | 285,260 |
| Mixed .. .. .. | 928,484 |
| Native .. .. .. | 7,805,515 |
| *Total* .. .. | 11,391,949 |

*Distribution of Population*:—

| | | *Total* | *Urban* | *Rural* |
|---|---|---|---|---|
| *European* .. .. | 1936 | 2,003,857 | 65·2% | 34·8% |
| | 1946 | 2,372,690 | 72·5% | 27·5% |
| *Non-European* .. | 1936 | 7,586,041 | 22·4% | 77·6% |
| | 1946 | 9,019,336 | 26·9% | 73·1% |

*Estimated non-European deaths*:—

We have applied the following mortality rates to respective population groups.

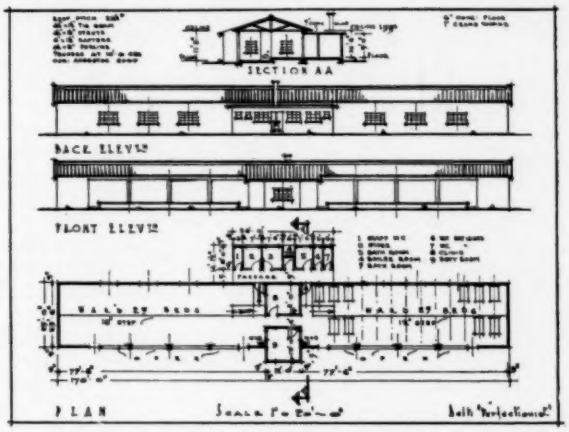
| | | *Estimated No. of Deaths* | *Actual Figures* |
|---|---|---|---|
| *Rural Natives* .. | 100 per 100,000 | 6,000 | 5,998 |
| *Asiatics* .. .. | 300 per 100,000 | 400 | 348 |
| *Mixed* .. .. .. | 500 per 100,000 | 4,500 | |
| *Urban Natives* .. | 800 per 100,000 | 10,000 | 14,452 |

*Total:* 20,900.

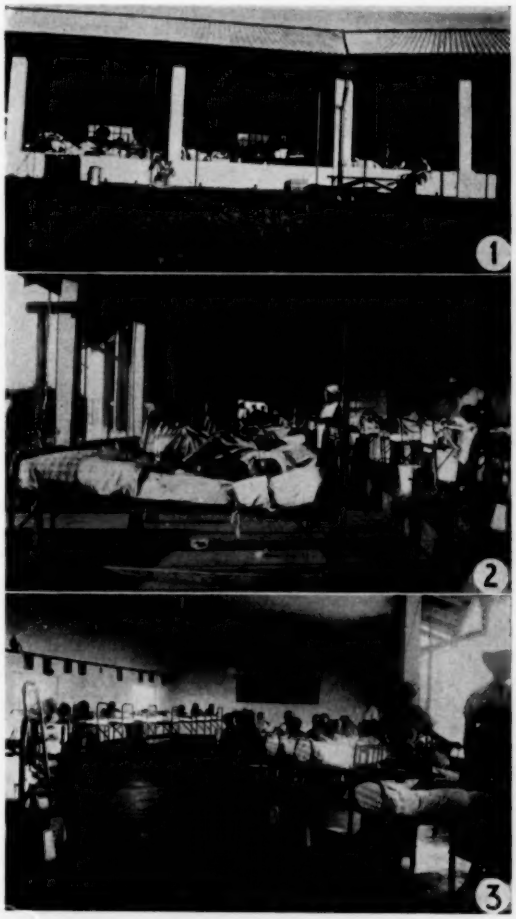
There already exists in South Africa some 4,000 beds for tuberculosis. If we are to build another 16,900 (say 15,000) beds at a cost of £2,000 a bed, i.e. 30 million pounds, we would contemplate national bankruptcy.

It is, however, quite possible to view the matter in a realistic and practical manner. A central 'core' for diagnosis and for active surgical treatment is necessary in any hospital and the rest of the beds should be of austerity type for isolation and convalescent purposes. After some years of experimentation with types of building and various kinds of building material I have erected at Umlazi Mission Hospital, some 15 miles south of Durban, a ward which cost £100 a bed equipped and which is suitable, with minor adjustments, for the whole continent of Africa.

The ward, which is illustrated in the following plan and photographs, is built of light concrete or brick. There is a back wall, with windows, two side walls and a front which is usually open, but which can be closed with blinds, windows, gauze, etc., to avoid inclement weather or insects.




Plan of Ward at Umlazi Mission Hospital




*Figs. 1-3.* Wards at Umlazi Mission Hospital

The floor is in two tiers so that the back row of beds looks over the top of the front beds. All beds face the open front and the view and the patients' impression is one of infinite space and freedom. Running is easy and community education or recreation is an integral part of the ward life. The Bantu people prefer this type of gregarious ward to any other and we have found that children particularly, no matter what their race, are happier in this type of hospital environment than in any other.

The capital cost for the total beds required for the Union would be £15,000 × 100, i.e. £1,500,000 plus staff quarters, kitchens, laundries, administration and the diagnostic and treatment 'core' so necessary for modern treatment. If we treble the estimated figures to allow for this a total of £4,500,000 is attained, a sum, if spread over a period of years, well within the pocket of this country.

As far as possible these wards should be added to existing hospitals which already possess the necessary facilities for diagnosis and treatment. In rural areas and native reserves, where no such institution exists, this type of ward could easily be added to Health Centres and the rural people isolated in their own environment. Cases for diagnosis and active treatment could be sent to more central institutions. Mission hospitals in rural areas are also suitable places for the erection of such wards.

Isolation hospitals are very necessary in primitive communities where there are many cases of tuberculosis whose hygienic habits leave much to be desired. If we are to cope with the problem of tuberculosis in Africa in a practical and economic manner wards of the type illustrated are essential.

### SUMMARY AND CONCLUSIONS

The cost of caring for the sick is becoming prohibitive. This is seen particularly in the cost of hospital buildings.

An estimate is given of the number of beds required in South Africa to isolate and treat cases of tuberculosis. The building of these beds at current costs (£2,000 a bed) is impossible.

An alternative type of ward is described and illustrated which can be built and equipped for £100 a bed.

Even if an expensive core for diagnosis and treatment is added the overall cost will not exceed £300 a bed.

This type of ward should be added wherever possible to existing institutions which already have adequate facilities for diagnosis and active treatment.

When such facilities do not exist these practical wards can be erected at Health Centres or Mission Hospitals and suitable cases referred to central institutions for active treatment.

Isolation hospitals for tuberculosis are essential in primitive countries.

# ACUTE HAEMOLYTIC DISEASE OF THE NEWBORN—ERYTHROBLASTOSIS FOETALIS*

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In this paper detailed reference will not be made to the immunological significance of the Rhesus factor. The following remarks will deal principally with the clinical aspect of the subject, based on personal experience in 52 cases in the past few years.

Though many hold that haemolytic anaemia is the essence of the disease, with consequent focussing of attention almost exclusively on the prevention and treatment of the anaemia, this concept cannot entirely explain the mechanism responsible for the development of oedema, hepatic damage, kernicterus, pancreatic changes and so on. In a way the older term erythroblastosis foetalis is better, for it at least suggests that a reaction may occur in various erythropoeitic tissues and that it starts in foetal life. We must also remember that we are dealing with an affected child and not merely with an interesting serological reaction occurring in the blood stream of the foetus and baby.

For convenience it has been customary to divide the varieties of this foetal and neonatal haemolytic disease into three clinical groups, namely:

*a*. Hydrops foetalis.
*b*. Icterus gravis.
*c*. Haemolytic anaemia of the newborn.

It must be remembered, however, that the underlying pathological processes are the same and that one group shades into the other.

### HYDROPS FOETALIS

When the foetus is severely affected in the uterus the various tissues become markedly oedematous; fluid accumulates in the pleural and peritoneal cavities and the umbilical cord and placenta are usually oedematous. The spleen and liver become grossly enlarged and a profound anaemia develops. Many immature red blood corpuscles and a very low haemoglobin content would most probably be detected in the circulating blood of the foetus, if it could be examined. Jaundice, however, is not a feature of this variety.

Foetuses with this form of the disease almost invariably die before birth or within the first few hours thereafter

* This paper was read at the Medical Congress of the Association held at Cape Town in September 1949.
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and treatment is of no avail. Autopsy reveals a striking degree of extra-medullary erythropoiesis.

### ICTERUS GRAVIS NEONATORUM

This may vary from an extreme type, clinically almost a hydrops, to a mild form with jaundice scarcely more pronounced than a physiological icterus.

In the very severe cases there may be oedema and commonly small ecchymotic haemorrhages may appear beneath the skin. The surface of the placenta, the amniotic fluid and the vernix caseosa may all be tinged yellow. The liver and the spleen are enlarged to a considerable extent. Though there is usually no icterus visible at birth this develops almost immediately thereafter and the skin may assume a deep saffron colour within a few hours. A number of these infants may survive if correct treatment is commenced promptly, but delay in such treatment will certainly result in the death of most.

In the more common intermediate type the infant appears normal at birth with possibly slight enlargement of the spleen. Icterus usually commences within the first 12 to 18 hours and the infant rapidly assumes the characteristic picture of a well-jaundiced baby with an enlarged spleen and liver. Merely a moderate anaemia may be present at birth, initial counts of blood possibly having a haemoglobin level as high as 14-15 grams %, or more and 4,000,000 red cells, but progressive cell destruction occurs and the haemoglobin level may drop to well under 10 grams % and the red cells to 2,500,000 or less within hours. There is evidence of erythroblastosis but the immature cells disappear relatively soon from the circulation, since extra-medullary erythropoiesis diminishes rapidly after birth. The white cells are increased, sometimes to a considerable degree, many myelocytes being present. The platelets may be considerably reduced at times.

It is quite possible that production of red cells is interfered with in these cases and the lowered count does not necessarily merely reflect continued blood destruction. One case in our series showed a transient aplastic picture in the bone marrow and peripheral blood but nevertheless recovered.

The icteric index (serum bilirubin) may be markedly raised. Haemoglobinaemia and haemoglobinuria are not found. The coagulation time may be increased and the bleeding time is frequently prolonged. Prothrombin is said to be lowered considerably so that haemorrhages may complicate the picture. It is probable that at times severe haemorrhages are due rather to thrombopenia; examination of the bone marrow in two of our cases with marked reduction of platelets revealed a depression of the megakaryocytes. The cerebro-spinal fluid is generally bile stained, but this finding is of no value either from the prognostic or diagnostic aspect.

The urine usually contains bilirubin. The excretion of bilirubin and its derivatives in the stools far exceeds the amount excreted by normal infants and the stools may appear a brick red at times. From the seventh to fourteenth day and sometimes later, the stool may become partially or completely acholic, but the colour gradually returns to normal after a few days. It is possible that a temporary obstruction occurs owing to blockage of the ducts with debris. Occasionally the stools remain acholic, this then being of severe prognostic omen, indicating obstruction, either through fibrosis and atrophy atresia of the ducts, or due to swelling of damaged hepatic cells which would lead to cirrhosis of the liver should the child live long enough. In our series in four instances death was associated with biliary obstruction, this occurring between the tenth and twentieth day after the commencement of treatment.

Very occasionally pigment stones in the main bile ducts may cause an obstructive jaundice.

As the illness progresses the child becomes listless, the jaundice deepens and the haemorrhages may appear. If death is to occur it usually does so within three days, attended with cyanosis and collapse. However, many infants in this group recover upon being efficiently treated. The blood commences to regenerate, the jaundice begins to fade and may disappear within two weeks, though in many cases it is found to persist much longer. The urine continues to be bile stained for a number of days after the fading of the jaundice. The liver and spleen may remain enlarged for many weeks.

Most of those recovering do so completely, but unfortunately some sustain cerebral damage, particularly of the basal ganglia (kernicterus), though not necessarily limited to these cerebral zones. In such instances the children may become handicapped by mental and physical defects arising from the cerebral lesions and it may take many months before these sequelae become recognised. Our own series fortunately demonstrated a low percentage of these neurological sequelae in infants who survived the initial storm. We have had only three such children in 52 cases and, as in the same group 13 died in the neonatal period, this represents a morbidity of kernicterus of less than 8% among the survivals.

A milder form of icterus gravis is occasionally observed. The jaundice appears only after a lag of 18 to 36 hours, the anaemia is less marked, fewer immature red cells are present and there is scarcely any hepatosplenomegaly. Though the jaundice may become quite pronounced it soon fades and usually disappears within seven to ten days. These cases are probably often wrongly labelled 'severe physiological'. Most recover without any specific treatment but some develop a degree of anaemia necessitating special measures.

### HAEMOLYTIC ANAEMIA OF THE NEWBORN

This is the variety of the disease probably least observed and noted. It is possible that many mild cases occur but are not recognised because of the absence of obvious symptoms and because the infant recovers before any marked cell destruction has been occasioned. The diagnosis may often not be made until the child is one or even several weeks of age and then is merely suspected because of marked pallor. The haemoglobin may have fallen to well below 10 grams % and the red cells to under 3,000,000. Immature red cells are not a feature. The spleen and liver are not usually enlarged. A careful enquiry will probably elicit the fact that there has been a mild jaundice. Further investigations will establish

the Rh status. The anaemia may progress and in severe cases the infant may die if transfusions are not instituted.

*Diagnosis.* Whereas at times a clear-cut clinical diagnosis may quite easily be ventured, the variability of signs and symptoms may render such diagnosis on other occasions, especially in mild cases, most difficult on purely clinical findings.

Presuming for the moment that we have no serological data on hand and that we have to be guided entirely by the clinical status, it might be said in general that if the icterus is actually present at birth and is of a severe degree, or if it becomes manifest shortly after birth and likewise becomes rapidly intense, the cause is most probably erythroblastosis foetalis, provided congenital syphilis is excluded. If it is known that the woman is Rh negative the diagnosis would certainly be more than presumptive.

It is true that the diagnosis often can be suspected because of the family history even before a patient is born, but there are many pitfalls. It must be stressed that pre-natal serological studies may be of value in determining the probability of erythroblastosis, but a positive diagnosis should seldom be made conclusively on these grounds and the precise serological diagnosis should depend rather upon the demonstration of an actual antigen-antibody combination in the newborn baby; the red cells coated with anti-Rh antibody of the blocking type would indicate this (Coomb's test).

It is in no way intended to belittle the practice of routine Rh status determinations on all young women and of antibody estimations during pregnancies. In an Rh-negative mother tests for antibodies should be undertaken at the first ante-natal examination, monthly thereafter until 32 weeks gestation and then fortnightly or even weekly.

A word of warning, however, could well be sounded against the non-discerning manner in which the whole subject would seem to be broached to so many women, with the possibility of evoking among a number a form of 'Rh hysteria', 'Rh phobia' or at times 'Rh mania'.

We must not spread unnecessary alarm among these women. Some doctors have been guilty of regarding an Rh-negative woman as inevitably condemned to still-births or to the bearing of an erythroblastotic infant. We must preserve our sense of proportion. Stress should rather be laid on the high degree of improbability of an iso-immunisation developing and one should merely pave the way for the more remote possibility of the condition occurring.

Our explanation of the affection should be of such a nature as to remove worry from the minds of the 'parents to be', to increase their confidence and gain their co-operation.

*Differential Diagnosis.* Many conditions may superficially and at times even profoundly resemble Rhesus factor erythroblastosis.

Examples noted by ourselves may be listed as follows:

1. Physiological icterus, if severe, especially in premature infants.
2. Congenital atresia of the ducts.
3. O.A.B. incompatibility—so-called 'icterus praecox'.
4. Hepatitis.
5. Syphilis.
6. Septicaemia.
7. Congenital familial icterus.
8. Renal vein thrombosis and infarction.

These all demonstrated a severe icterus or erythroblastosis or combination of both, and required complete routine investigation together with accurate clinical assessment in order to differentiate at times.

It might here be added that erythroblastosis arising in some of these other conditions does not necessarily indicate a severe prognosis. This was well illustrated in a case of congenital lues with a marked erythroblastosis but in whom recovery was rapid on appropriate anti-luetic measures.

Further conditions which presented a certain amount of diagnostic difficulty on occasions, because of a combination of physiological icterus and respiratory or cerebral symptoms, were the following:

1. Birth injury.
2. Neonatal asphyxias.
3. Haemorrhage.

It does not fall within the compass of this paper to consider these other illnesses apart from mentioning their occurrence: but it will be appreciated that if an infant presents signs or symptoms indicating any of the above-mentioned conditions, this necessitates a prompt and complete examination and investigation.

*Complications.* These are a major factor in producing death in erythroblastotic infants and must be anticipated whenever possible. Those chiefly met with are:

1. *Haemorrhage.* This may be due to several factors:
   *a.* Hypoprothrobinaemia. Probably less common than generally believed.
   *b.* Thrombopenia. Probably more often the cause than is generally realised.
   *c.* Increased capillary fragility.
2. *Prematurity.*
3. *Obstructive jaundice and liver failure.*
4. *Neurological sequelae.*
5. *Intercurrent infections.*
6. *Diarrhoeal Disorders.* Probably associated with the hepatic derangement.
7. *Hypoglycaemia.* ? due to hypertrophy of the islets of Langerhans.
8. *Hypothermia.*

*Prognostic Criteria.* Based upon personal observation of this series of 52 cases it has been possible to form a reasonably fair opinion of the prognostic value of certain signs and symptoms. These are accordingly quoted here.

*Jaundice.* This was the most commonly noted of the main features. The actual intensity of the jaundice could not always be taken as an index of the severity but the time of onset of icterus certainly could; if present at birth or very shortly thereafter the outlook was much graver.

The severity of the icterus could not be definitely correlated with the type of maternal antibody nor with the development of kernicterus. Latterly, however, one's impression has been that a severe icterus is generally associated with a high titre of blocking antibodies.

*Anaemia.* Many were not anaemic at birth but most developed some degree of anaemia while under obser-

vation. No correlation could be found between the degree of anaemia and that of jaundice.

The eventual degree of anaemia was not in itself an index of the severity of the disease, but if a severe anaemia was present at birth, with low haemoglobin levels on the first day the outlook was always found to be serious. Kernicterus would not seem to be dependent on anaemia as such, but undoubtedly there seems to be some correlation between the severity of the haemolytic process and the incidence of kernicterus.

*Erythroblastaemia.* If pronounced at birth always signified a severe case.

*Splenomegaly.* This was present to a varying degree in all cases. If pronounced it was invariably found to be associated with a marked erythroblastotic count, provided the blood was examined within a couple of days of birth, for the erythroblasts disappeared rapidly from the circulating blood after the first few days. A markedly enlarged spleen at birth usually heralded a stormy passage.

*Hepatomegaly.* Some enlargement was noted in every case. If marked, it betokened a good deal of trouble, at least a difficult and protracted convalescence. Most kernicterus cases had large livers.

*Oedema.* If appreciable was always of severe prognostic significance. Mildest degrees of oedema were often first seen on the face.

*Respiratory Disturbances.* Cyanosis, disturbances of rhythm, irregular grunting, were always found to be of severe portent. Recently Zuelzer has stated that the only single symptom which enabled him to predict a fatal outcome with more than 50% probability was respiratory difficulty.

*Nervous System.* Listlessness, neck rigidity, opisthotonus, twitching, alternating muscular rigidity and flaccidity, weak cry or high-pitched shrill cry, vomiting, poor sucking reflex were all of significance; neurological signs were certainly more often noted in fatal cases, but the presence of these signs and symptoms *per se* did not necessarily denote a severe prognosis in terms of actual survival, though they certainly did herald a kernicterus in several instances. Of these nervous signs opisthotonus would appear to be followed more frequently by cerebral sequelae than any other single nervous sign. The immediate cause of death in those children dying at two to five days of age seemed generally to be medullary failure consequent upon cerebral damage.

It must be remembered that these various manifestations were observed by us in infants in whom the treatment, in most cases, consisted, *inter alia*, of simple transfusions. As previously indicated our mortality in these has been one of 25%. It remains to be seen to what extent exchange transfusions will influence these findings; the reported experience of well-known investigators overseas, including Diamond, Wiener, Mollison and others, appear to reveal modification in many instances.

We have at this stage had an exchange transfusion done only in three of our cases. These all recovered and did well, but they were not severe cases. The opportunity was taken in twins (dissimilar but both apparently equally afflicted with the disease) to give a simple transfusion in one and an exchange transfusion in the other. Both did equally well.

Apart from clinical findings other factors can be considered in attempting to assess the prognosis, such as family history and laboratory findings. One must stress that for the present it would be wiser to be guided by Diamond's statement that a prognosis based on antibody tests must, as yet, be offered with reservation.

## TREATMENT

*Prophylactic.* Indiscriminate transfusions into all Rh-negative women should be avoided, this applying even to intramuscular injections of blood. Rh typing should first be done or in emergencies Rh-negative compatible blood should be used.

*General Management of a Suspected Case.* If it is known that a woman has previously had an erythroblastotic child, particularly if this child has died from the disease, and if during the present pregnancy there is a rising titre of antibodies, it is wise to presume that the expected infant will reveal Rh disease, although in fact it may not, and thus prepare beforehand for emergency treatment at birth.

When there is no history of former erythroblastosis the finding of antibodies in the mother's serum is still more significant and an Rh baby must be anticipated, but again it must be stressed that pre-natal serological studies though of great value in determining the probability of erythroblastosis do not necessarily permit positive diagnosis on such grounds, that is to say when guided by tests at present available to us.

*Obstetrical Measures.* Considerable difference of opinion exists in regard to the criteria for interrupting a pregnancy and the optimal time of gestation at which this should be done.

Some advocate termination of pregnancy as soon as the foetus becomes viable in an endeavour to prevent further passage of antibodies from mother to foetus; this has been particularly recommended if the titre of Rh antibodies in the maternal blood is found to rise suddenly. *This radical procedure, however, would seem to be quite unjustifiable.* The rise in titre may be merely an anamnestic reaction if a mother has been previously sensitised and the present pregnancy may represent an Rh-negative child from a heterozygous father, so that a normal infant would have its birthright of complete gestation removed and be thus subjected to the hazards of marked prematurity. Recently we personally experienced such a case of anamnestic reaction. Despite a rising titre of antibodies the obstetrician was requested to allow the pregnancy to go the full term. As a precaution a team stood by ready to give the expected infant an exchange transfusion immediately after birth, but a healthy Rh-negative baby arrived on the scene.

Even granted that the expected infant happens to be afflicted with the antigen-antibody reaction this does not with certainty mean that the disease will be severe.

Each case should be considered entirely on its merits and we must certainly avoid producing undue prematurity, particularly as the hazards of such are enhanced by the very nature of the Rhesus affection, with its in-

creased tendency to bleed, susceptibility to cerebral trauma, etc.

The following would, therefore, seem to be a reasonable procedure:

*a.* Rh-negative women who show no sensitisation should naturally be allowed to go to full term.

*b.* Mildly-sensitised women—where no blocking antibody or only low titres of this are found—should be delivered at full term and the infant be treated expectantly.

*c.* In more severely sensitised women—as judged by a high or sudden rising titre of blocking antibody, especially if there is a history of previous erythroblastotic mortality—it would possibly be justifiable to anticipate full term by a period of two to three weeks. Reasonable certainty of the husband being homozygous would support this action. If there is any doubt, however, it would be better to deliver at full term and treat the infant expectantly, as it is not yet certain that premature delivery influences the prognosis favourably.

Differences of opinion also exist in regard to the correct method of delivery—namely, by medical or surgical induction, or by Caesarean section. Here again it is perhaps wise to consider each individual case with its attendant circumstances, weighing the disadvantages of prolonged parturition due to induction against those of Caesarean section, which in fact may be found to have been unnecessary.

If any anaesthetic be given to the mother this should be of such a nature as to permit adequate oxygen saturation of the foetal blood, since the infant is likely to be anaemic.

The cord should be tied promptly after delivery to prevent additional blood, containing maternal antibodies, being compressed into the foetal circulation from the placenta by the uterine contractions. Transfer of placental blood, when it is allowed to occur, may also throw too great a load on the infant's circulatory system, if there is a severe anaemia.

*Assessment at Birth.* The clinical features have already been discussed. The Coomb's test and the Rhesus status of the infant must be ascertained. The cord haemoglobin and bilirubin and the blood count should be estimated.

Recently Mollison and Cutbush have demonstrated the value of determining the haemoglobin and bilirubin in assessing whether an infant requires prompt transfusion or not.

They maintain that if the cord blood contains above 14.5 grams % Hb the infant is very likely to recover without treatment, if below 8 grams % to die within 24 hours, despite treatment, including exchange transfusion. These latter cases show a raised venous pressure and probably die from cardiac failure. Anything below 14.5 grams % Hb in the cord blood at birth would call for prompt treatment.

Estimations for haemoglobin at birth should be done on cord blood. It must be remembered that venous blood Hb is higher than that in the cord and capillary higher than venous. Thus 18 grams % Hb in capillary blood taken from an infant a few hours after birth does not exclude the possibility of an anaemia at the moment of birth.

According to Mollison and Cutbush bilirubin in the cord blood, if below 3 mgm. per 100 c.c. almost always betokens recovery; if between 3 and 4 mgm. indicates that most will recover (80-90%); if above 4 mgm. heralds a severe prognosis and denotes at least half will die.

The bilirubin content is a less reliable index of the prognosis than is the haemoglobin content, and is still less so in the venous blood after one to two days, but it is usually high in fatal cases.

Cord bilirubin and cord haemoglobin assessed in conjunction form a more reliable index.

This combination of clinical appraisement and haematological estimation must at present play a greater part than the ante-natal serological findings in determining the course of treatment to be followed at birth.

### THERAPEUTIC MEASURES

*Blood transfusions.* Whereas indiscriminate blood transfusions should not be given, it is felt that if there is any reasonable doubt it is better to transfuse early.

Whatever method of transfusion is employed the infant's blood state must be carefully watched and during the first few days the red cells should not be permitted at any time to fall below a level of 3,000,000 per c.mm., nor the haemoglobin to decline lower than 8-10 grams %. The latter should be maintained at 12 grams % in the first week, if possible. It is known that infants can be quite well at lower levels than these but, in view of the fact that in haemolytic disease sudden crises can occur with dramatic reduction of the red cells and haemoglobin, it is better to aim at having a reserve.

*a.* Simple Transfusion: For this, Rh-negative blood is required and if the procedure is initiated within a few hours of birth the umbilical vein can be used; thereafter one of the superficial veins of a limb or the scalp must be employed for a 'push-in' or alternatively a 'cut-down' must be done on one of the usual limb veins. Whichever of these is utilised it has been found preferable by us to use a slow drip transfusion, thus permitting the use of at least 15 to 20 c.c. per pound of body weight as contrasted with 10 c.c. recommended for the rapid transfusion method. As a rough guide the average infant requires 35-40 c.c. blood to raise the Hb by 10%. Introduction of a larger volume rapidly would be fraught with danger, the anoxic myocardium not being able to tolerate this overloading of the circulation. Pulmonary oedema is easily developed; thus the blood and other fluid intake must be controlled. Provided treatment has been initiated within the first two days and large transfusions have been used, we have seldom found it necessary to give more than two transfusions to those who did not actually die within the first three days; occasional infants have needed a number of transfusions.

*b.* Exchange Transfusion: If during the early stages of the disease the infant's blood is drained off and simultaneously replaced with compatible Rh-negative blood, it is reasoned that the morbid process should at least be considerably decreased, if not promptly aborted.

To secure this several methods of exchange or replacement transfusion have been advocated, and whichever is used the process of bleeding and of infusion is carried

out simultaneously until a minimum 500 c.c. is exchanged in a new-born infant, the procedure producing an 80% to 85% replacement of the infant's blood during the one to one and a half hours that is required for this method. Recently Wiener has advocated using 1,000 c.c. of blood in more severe cases, and thereby claims a 98% replacement.

At the end of the transfusion one should leave about 50 to 75 c.c. more blood in than has been actually extracted. To combat the possible alkalotic tetany that might be produced by an excess of sodium (sodium citrate being used to prevent clotting) it is wise to give slowly an injection of calcium (5 c.c. of 10% calcium gluconate) intravenously. Fresh blood should be used for these cases, if at all possible, in preference to bank blood. Antibiotics and chemotherapeutics, such as sulphadiazine and penicillin should be given for 48 hours to counteract a possibility of infection per apparatus.

It must be stressed that not every infant with possible erythroblastosis requires exchange transfusion. The indications for this procedure must be clear. It is a relatively new method of treatment and therefore standardised criteria could scarcely as yet be expected from the various exponents, but it would seem evident that the decision to use it or not must rest with clinical and haematological assessment at birth, rather than with knowledge of the ante-natal serological determinations.

The absence of clinical evidence and of clear-cut laboratory findings of free and bound antibody in the infant would suggest that the outlook is in any case good, and drastic treatment not necessary.

Preliminary statistics from reliable clinics seem to indicate a lowering of mortality in the group of severe cases by this use of exchange transfusion, but one disappointing feature would appear to be the fact that kernicterus is not thus avoided, at least when judged by Diamond's relatively large series of cases. This method of transfusion may possibly present a most useful measure but its application must not be abused and until many well-controlled observations have been recorded there can be no certainty of the extent to which blood replacement really influences the 'all over' prognosis.

*Additional Measures.* During the actual transfusion, when a relatively large number of red cells are introduced in a short space of time, it would be rational to give extra oxygen and it has been our practice to use an oxygen tent with a flow of four to six litres per minute, as long as there is any clinical tendency to cyanosis. Those cases presenting the respiratory signs referred to earlier in this paper would warrant oxygen administration owing to the actual respiratory difficulty.

The haemorrhagic tendency in the severe cases of this disease is often due to platelet deficiency, for which the fresh blood transfusion would be the most efficient form of treatment. We have seldom found a prothrombin deficiency, contrary to what would be expected in cases with hepatic derangement and it is questionable whether vitamin K would be of any more use than the transfused fresh blood to combat this, but it is nevertheless advocated and routine injection of this for the first two days would certainly not be contra-indicated.

Further treatment must include the following:

*a.* Measures to correct the anaemia, apart from the actual transfusion.

*b.* Treatment to assist any hepatic disturbance.

*c.* General supportive treatment with special care and attention for prematures.

*d.* Treatment to guard against intercurrent infection to which these infants are unduly susceptible.

Time does not permit detailed discussion of these, but it will be evident that oral administration of iron and appropriate vitamins, injection of crude liver, exhibition of antibiotics and possibly sulpha-drugs, judicious selection of food formulae with raised protein content, careful nursing and protection from intercurrent infection and hypothermia must all play their part.

Owing to the finding of antibodies in some specimens of milk it is generally advocated that these infants should not be breast fed by their mothers, but the cases where anaemia has apparently been maintained through absorption of antibodies are so few as to warrant disregarding this factor. We have done so lately in several cases without any untoward effect. However, if one wishes to exercise caution the mother's milk can be expressed and boiled, which procedure probably destroys the antibodies. After two weeks the maternal milk should be tested for antibodies, and eventually it may be found possible to feed at the breast if the production of milk has been maintained.

Cyanosis and apathy without evidence of intra-cranial lesions lead one to suspect low blood sugar, calling for appropriate measures.

From the aforementioned it must be evident that the therapy for erythroblastosis is drawn from many facets of medical knowledge; it has been rightly said by Wheeler that 'though the condition is a fascinating disease immunologically we must not forget our paediatrics when we go to treat it'.

It is possible that the advent of exchange transfusion may now modify a good deal of the treatment at present advocated for these cases, but it cannot be considered a panacea. It has yet to be shown more conclusively that this method appreciably influences the manifestations of toxicity should these have already appeared. There still remains a necessity for close co-operation between serologist, general practitioner, obstetrician and paediatrician.

One must plead for routine ante-natal testing so that when suspicion of maternal sensitisation arises everything may be 'teed-up' for prompt treatment at birth, if required. The theme throughout this paper, however, is to stress the importance of clinical and haematological assessment of the infant actually at birth. It is this that should guide us in the selection of the treatment.

Prevention of antibody formation in the mother would be better than care of the disease in the child, but until medical science has evolved such a possibility, we must realise that our strongest weapon in severe cases lies in prompt treatment at birth and efficient handling in the neonatal period.*

* The cases on which this article is based were treated by Dr. S. N. Javett and myself mostly at the Transvaal Memorial Hospital for Children, but some were handled at the Maternity Homes. My thanks are due to Dr. Javett for making his clinical material available to me.

ADDENDUM

After this paper was read to Congress some further interesting facts in regard to blood transfusion therapy were published by Diamond and his associates and more recently by Pennell.

Allen, Diamond and Watrous state that a study of 205 babies with erythroblastosis foetalis indicated beyond reasonable statistical doubt that exchange transfusion of blood from female donors resulted in a lower mortality than that from male donors. The beneficial component of this blood is not known but further studies are being conducted on isolated plasma factors.

Pennell reports the case histories of 28 patients with erythroblastosis foetalis treated by the transfusion of compatible sedimented red cells from rhesus negative bank blood. He claims that this method, in contrast to that of exchange transfusion, reduces the administration of plasma to a minimum, thereby preventing the further haemolysis of the infant's red cells by some activating substance believed to be present in adult plasma.

Pennell holds that 50 to 60 c.c. amounts of these sedimented red cells are sufficient to cause an adequate rise in haemoglobin levels with relatively no load being thus thrown on the infant's circulation. Further, excessive amounts of extraneous substances, such as sodium citrate, need not then be given. He maintains that the process is a simple one, not dependent upon the expert technique required for an exchange transfusion or the elaborate laboratory facilities required for a transfusion of washed maternal red cells.

In his series Pennell quotes a mortality rate of 10.7% in those patients transfused with sedimented red cells, which certainly compares favourably with other reports in regard to exchange transfusions.

Should Pennell's method prove as universally effective as he himself found to be in his own reported cases, this simple and probably safer procedure should certainly replace the more elaborate measures now being used.

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# OBSERVATIONS OF THE GENERAL INCIDENCE OF CERTAIN SIGNS USUALLY CONNECTED WITH THYROTOXICOSIS

## WITH SPECIAL REFERENCE TO 'LID LAG', (VON GRAEFE'S SIGN)*

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During recent observations on the coincidence of hyperthyroidism and peptic ulcer it was noticed that a high proportion of patients with the latter complaint showed Von Graefe's sign (lid lag), one of the characteristic ocular phenomena of thyrotoxicosis. This sign was first described by Von Graefe in 1864 saying '. . . *namentlich folgt bei Senkung der Cornea das obere Augenlid nicht*'. He remarked that it was not the result of exophthalmos, being present in early cases of thyroid disease which showed no proptosis. He considered that it was a sign pathognomonic of hyperthyroidism in the early stage '. . . . *geringen Grade der Krankheit einen pathognomonischen Werth hat*'. It is now recognised that the sign is not peculiar to thyrotoxicosis (Eason, 1927) and may occur in normal people (Joll, 1932). Joll remarks that it also occurs in all forms of goitre, in myotonia congenita, and in all cases of proptosis.

It was thought of some interest to determine the approximate incidence of lid lag in people without thyroid disease and to see whether this sign was particularly common in cases of peptic ulcer or whether its having been noticed in this connection was merely an expression of its general occurrence. In this investigation 600 people of all ages and approximately equal sex numbers who attended a general hospital have been examined. All patients with dysthyroidism, severe illness, and prolonged pyrexia have been excluded. Otherwise there has been no selection except that 37 extra cases of peptic ulcer have been specially included. At the same time certain other manifestations which occur in thyrotoxicosis were also looked for in this series. The subjects were questioned with regard to preference for hot or cold weather and excessive sweating. Lid lag, lid retraction, exophthalmos, enlargement of the thyroid gland, and tremor of the outstretched fingers were looked for. The heights and weights of all subjects over 18 were noted down where practicable.

For present purposes 'lid lag' is defined as occurring when a white band of sclera appears between the upper lid and the cornea on following a moving object down wards with the eyes. If 'lid retraction' is present lid lag can only be considered to exist if there is a definite widening of the band of sclera already visible. This is

* This paper was read at the Medical Congress of the Association held at Cape Town in September 1949.

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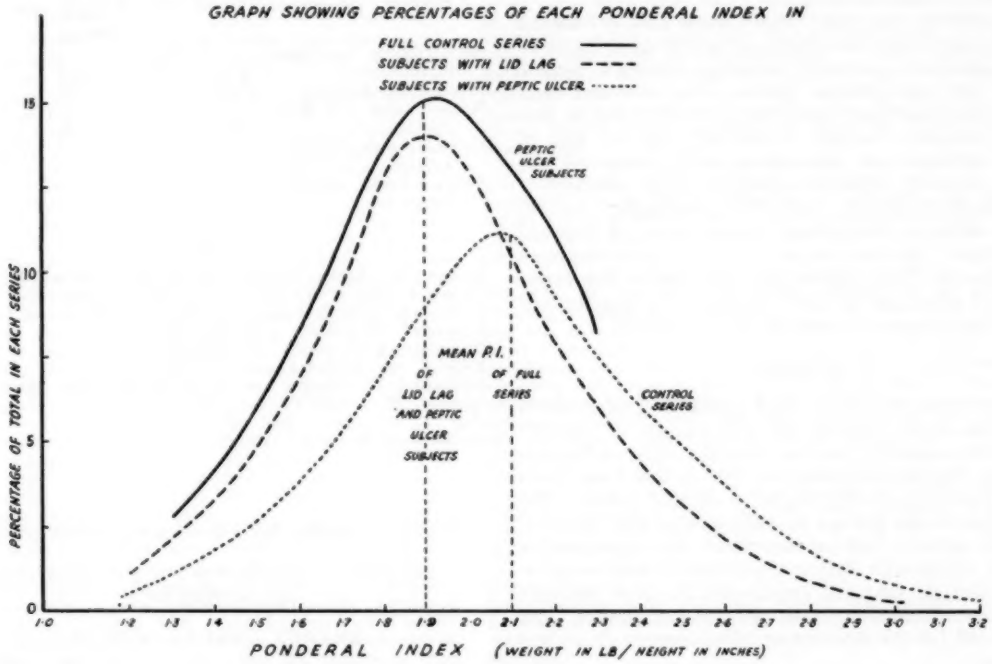
the most objective way of defining lid lag, although it is evident that there may be a degree of lagging of the upper lid, in people whose lid is usually held at a low level, without any sclera coming into view.

*Results.* (See Table.)

*Type of Eyelid Movement.* All cases of lagging of the upper eyelid were not alike. The band of sclera might appear during the whole movement of the eyeball, or any part of it. In other words the lag might commence as soon as the eyeball started to descend, or the lid might move normally at first, but lag later. The movement might be smooth or jerky. The lag in some cases was variable, at times being marked and at others not elicited at all. In five cases it was unilateral, and in two there was actually a reverse or upward movement of the eyelids as the eyeballs started downward. In one person the lid retraction was unilateral.

Eight of the 14 subjects with lid retraction also showed lid lag, as did all three with exophthalmos, and five out of the 35 people with simple goitres.

The total number of patients with peptic ulcer was 76, and of these 23 (33%) showed lid lag. This incidence is significantly higher than that of lid lag in the control series (10%). Now the impression had been formed that lid lag was more common in thin people, and since peptic ulcer characteristically occurs likewise in people with low ponderal index (P.I.) (Draper, 1932; Robinson, 1938), this was suspected of being the explanation of the frequent occurrence of lid lag in ulcer subjects. To test this hypothesis the P.Is.* of all subjects over 18 were worked out, and all fell between 1.2 and 3.2. The number of subjects pertaining to each index was noted and expressed as a percentage of the whole. Thus two subjects (0.5% of the total) had a P.I. of 1.3. These


GRAPH SHOWING PERCENTAGES OF EACH PONDERAL INDEX IN
FULL CONTROL SERIES
SUBJECTS WITH LID LAG
SUBJECTS WITH PEPTIC ULCER
PEPTIC ULCER SUBJECTS
CONTROL SERIES
MEAN P.I. OF LID LAG AND PEPTIC ULCER SUBJECTS
MEAN P.I. OF FULL SERIES
PERCENTAGE OF TOTAL IN EACH SERIES
0
5
10
15
1·0 1·2 1·3 1·4 1·5 1·6 1·7 1·8 1·9 2·0 2·1 2·2 2·3 2·4 2·5 2·6 2·7 2·8 2·9 3·0 3·1 3·2
PONDERAL INDEX (WEIGHT IN LB/HEIGHT IN INCHES)

*Lid Lag in Relation to Other Observations.* The male sex predominated in the proportion of 2 : 1. All decades produced subjects with lid lag, but it was more common over 40, as the following table shows.

Table showing Age Incidence of Lid Lag

| *Decade* | *Total Subjects* | *Lid Lag* | *Lid Lag %* |
|---|---|---|---|
| 0/9 .. .. .. .. | 31 | 3 | 9.0 |
| 10/19 .. .. .. .. | 50 | 2 | 4.7 |
| 20/29 .. .. .. .. | 50 | 2 | 4.0 |
| 30/39 .. .. .. .. | 72 | 8 | 11.0 |
| 40/49 .. .. .. .. | 115 | 20 | 17.4 |
| 50/59 .. .. .. .. | 132 | 22 | 16.6 |
| 60/69 .. .. .. .. | 107 | 21 | 19.6 |
| 70/79 .. .. .. .. | 43 | 7 | 16.0 |

percentages for each P.I. referring to (1) all the subjects (2) the peptic ulcer subjects, and (3) those showing lid lag were plotted separately on a single graph. The mean P.I. in the full control series was 2.1 (slightly in excess of the mode), while that of the subjects with peptic ulcer and those showing lid lag was 1.9 in each case. This graph thus confirms the tendency for lid lag to occur in people of slim build, but it seems unlikely that this factor alone can explain its excessive appearance in peptic ulcer subjects. However the similarity in male preponderence in both peptic ulcer (about 4 : 1—

* Ponderal index in this investigaton is calculated by dividing the weight in pounds by the height in inches, and expressing to the first place of decimals.

Stewart, 1923; Ryle, 1932; Tidy, 1944; Sallstrom, 1945) and lid lag (2 : 1 in this series) may also offer a partial explanation.

*Other Findings.* The occurrence of 35 cases of markedly enlarged non-toxic thyroid glands in subjects resident in Birmingham puts the approximate rate of simple goitre in this city at 5.9%.

It was mildly interesting to observe that 125 people preferred cold weather, 273 hot weather and the remainder were indifferent. All subjects under 20 preferred the heat. Only therefore in young people can preference for cold weather be considered an important diagnostic feature in borderline hyperthyroidism, unless there has been a recent change in preference.

Assertions by subjects of excessive sweating were not uncommon, but revealed nothing of particular interest. The very fine rapid tremor generally considered characteristic of hyperthyroidism was found 11 times in the whole control series.

*Mechanism of Lid Lag.* Von Graefe (1864) believed that the cause of his described sign was a disturbance of lid musculature, probably affecting Müller's muscle through the sympathetic system. He observed that morphia abolished the sign. Pochin (1939) believed that the lid retraction (usually combined with lid lag) in Graves' disease was associated with spasm of the levator palpebrae superioris and not with affection of the involuntary muscle. Joll (1932) considered that lid lag was often a 'mechanical consequence of forward displacement', but this cannot explain its occurrence in normal people. The observations reported in this paper do little to elucidate the mechanism of the lagging, but suggest that it is more common in thin people.


## SUMMARY

It had been noticed that a high proportion of patients with peptic ulcers showed the sign known as 'lid lag'. Von Graefe originally believed that this sign was pathognomonic for hyperthyroidism, but it has long been realised that it may also occur in normal people. The main object of the present investigation of 600 'control' euthyroid subjects was to determine the approximate incidence of this sign among the populace and to ascertain whether its frequent appearance in ulcer patients was merely a reflexion of its general occurrence. The criteria used for the assessment of lid lag are described in the text.

An analysis of the results obtained showed that the incidence of lid lag among the full 600 subjects was 14% (10% not including subjects with peptic ulcer), while in the peptic ulcer group it was 33%, a significantly large difference. Lid lag was observed in all decades, but was apparently more common over the age of 40. It was commoner in males than in females in a ratio of 2 : 1; a markedly different sex incidence from the female preponderance of dysthyroidism. Use of the 'ponderal index' (weight/height ratio) revealed that lid lag was more common in thin people, although it was noted with all ranges of ponderal index. The mean P.I. of the peptic ulcer patients and of all subjects with lid lag was the same, being lower than in the full 'control' series. This observation, together with the similarity in the sex incidence of lid lag and peptic ulcer, helps to explain the high percentage of ulcer patients who showed lid lag.

Among the 600 people examined lid retraction was observed 14 times and exophthalmos three times. A fine tremor of the outstretched fingers was seen in 11 subjects. A preference for hot weather rather than cold was not marked, except in children (and this was in the English Midlands). Thirty-five people had obvious simple goitres, although Birmingham is outside the endemic area.

Nothing new regarding the mechanism of lid lag or lid retraction is presented, but the conclusion from this small investigation is that Von Graefe's sign is so common in normal people that it cannot be relied on to give much help in the diagnosis of hyperthyroidism.


| | *Total* | *Percentage of All Subjects* | *With Lid Lag* | *Percentage with Lid Lag* |
|---|---|---|---|---|
| All Subjects .. .. | 600 | — | 85<br>Male 58<br>Female 27 | 14 |
| All Subjects omitting Peptic Ulcers .. | — | — | — | 10 |
| Peptic Ulcer Subjects.. | 76 | — | 23 | 33 |
| Subjects with Lid Retraction .. .. | 14 | 2.3 | 8 | 57 |
| Subjects with Exophthalmos .. .. | 3 | 0.5 | 3 | 100 |
| Subjects with Simple Goitre .. .. | 35 | 5.6 | 4 | 12 |

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# ASSOCIATION NEWS : VERENIGINGSNUUS

## BRITISH COMMONWEALTH MEDICAL CONFERENCE

### SECOND ANNUAL MEETING

### BRISBANE, 23-25 MAY 1950

REPORT BY THE MEDICAL SECRETARY, DR. A. H. TONKIN

The Second Annual Meeting of the British Commonwealth Medical Conference was held in the Choral Room of Lennon's Hotel, Brisbane, Queensland, Australia, commencing at 9.30 a.m., 23 May 1950, and concluding at 5.30 p.m., 25 May 1950.

The Officers of the Conference were:—

*Chairman*: Sir Victor Hurley, President, British Commonwealth Medical Conference, and President, Federal Council of the British Medical Association in Australia.

*Deputy Honorary Secretary-Treasurer*: Dr. A. Macrae, Deputy-Secretary, British Medical Association (deputising for Dr. Charles Hill).

*Local Organizing Secretary*: Dr. J. G. Hunter, General Secretary, Federal Council of the British Medical Association in Australia.

The Delegates present were:—

*Australia*: *Dr. H. R. R. Grieve* (Member of the Federal

Council of the British Medical Association in Australia, Undercliffe, Sydney, N.S.W.); *Dr. A. E. Lee* (Member of the Federal Council of the British Medical Association in Australia, Wickham Terrace, Brisbane, Queensland).

*Canada*: *Dr. Harris McPhedran* (Chairman of General Council, Canadian Medical Association, Medical Arts Building, Toronto 5, Ontario); *Dr. T. C. Routley* (General Secretary, Canadian Medical Association, 135 St. Clair Avenue, West, Toronto 5, Ontario).

*Great Britain*: Dr. E. A. Gregg (Chairman of Council, British Medical Association, Tavistock Square, London, W.C. 1, England).

*India*: *Dr. S. C. Sen* (Honorary Secretary, Indian Medical Association, 1 Barakhamba Road, New Delhi, India).

*New Zealand*: *H. K. Pacey, Esq., F.R.C.S.* (Honorary General Secretary, British Medical Association, New Zealand Branch, Box 156, Wellington, New Zealand.

*Pakistan*: *Dr. N. Ahmed* (President, Pakistan Medical Association, Chittagong, East Pakistan).

*South Africa*: *Dr. A. H. Tonkin* (Medical Secretary, Medical Association of South Africa, 35 Wale Street, Cape Town, South Africa).

*Southern Rhodesia*: *Dr. G. A. Jamieson* (4 Chilham Court, P.O. Box 552, Bulawayo, Southern Rhodesia).

Apologies were received from the Ceylon and Eire Medical Associations.

The Chairman, in extending a warm welcome to the delegates, expressed regret that the representatives of Ceylon and Eire had not been able to be present.

The Chairman then referred to the purpose for which the Conference had been established and said that it was true to say that much of the present unsettled state in world affairs was very largely due to lack of knowledge and appreciation among the nations of the special national problems affecting every country. This was mainly due to disturbed conditions following the War, and it was felt that in the solution of these problems the medical profession could play a part not only from the medical point of view but also from the point of view of the general welfare of the community. In the field of medicine fraternal relationships existed between members of the medical profession and they thus could exercise considerable influence for good quite out of proportion to their actual numbers. Conditions of life and work varied considerably in the different countries but human nature was much the same the world over; the real value of any new theories or plans could best be judged by practical experience and the assessment of the results which followed their application.

The papers and addresses to be given at the meeting would outline how some of the medical and social problems were being dealt with in Australia. It might be that the visiting delegates would learn something of value, and Australia certainly hoped to learn from them in the exchange of views.

The Chairman then read a message of greeting from the Medical Association of South Africa, and the delegates present also conveyed warm greetings from their Associations.

A. *General Business*: 1. *Sharing of Expenses of Meeting.* In a letter forwarded several months previously to constituent associations Dr. Charles Hill, the Honorary Secretary-Treasurer, submitted a tentative estimate of the expenses of the Conference, and in doing so made the suggestion that if any delegate were not present and the expenses were thus reduced, the amount of the reduction be credited to Great Britain, who carried the heaviest load. In this statement it was estimated that the total expenses, including subsistence of £3 sterling per day, would work out at £4,305. This amount included a total of £893 for Ceylon and Eire. Taking the total of £4,305 and allotting it on the basis agreed upon at Saskatoon, the proportion worked out as follows:—

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Australia ... ... | £538 | 3 | 0 | India ... ... ... | £86 | 2 | 0 |
| Canada ... ... | £602 | 14 | 0 | New Zealand . | £236 | 15 | 0 |
| Ceylon ... ... | £43 | 1 | 0 | Pakistan ... ... | £43 | 1 | 0 |
| Eire ... ... ... | £129 | 3 | 0 | South Africa . | £279 | 17 | 0 |
| Great Britain . | £2,303 | 3 | 0 | S. Rhodesia ... | £43 | 1 | 0 |

Deducting from £893 the sum of £152 4s., representing the allocation to Ceylon and Eire of their share of the total, which it was assumed they would not be asked to pay, the net surplus would be £720 16s. Deducting this amount from Great Britain's share would mean that Great Britain would be required to pay £1,583 7s. It was unanimously agreed to accept this arrangement of the sharing of the costs.

2. *Future Meetings of the Conference.* (a) It was decided to accept the invitation of the Medical Association of South Africa to hold the next Conference at Johannesburg on 11-13 July 1951.

In regard to this Conference it was decided to recommend to the constituent Associations that the Meeting be spread over four days, the first and last sessions to be free of formal papers.

(b) It was decided that the question of holding meetings subsequent to the meeting in South Africa in 1951 be referred to the constituent Associations for consideration, having regard particularly to the fact that an invitation had been extended by the Indian Medical Association to hold a meeting in India, preferably in 1952, or in 1953, and also that it was the desire of the New Zealand Branch of the British Medical Association to hold a meeting in the near future in New Zealand.

3. *Assistance to Constituent Member Nations.* A communication was received from the Pakistan Medical Association suggesting that the British Commonwealth Medical Conference might devise ways and means to enable the National Medical Associations of the Commonwealth countries to act as a single body in an emergency to come to the help of the country of a member association, e.g. during severe epidemics or any catastrophe like an earthquake, or in the event of aggression by another nation. It was suggested that help might be forthcoming by, *inter alia*, supply of drugs and equipment, the sending of medical missions, and approaching national and international organizations, such as the Red Cross, World Health Organization and the World Medical Association.

After very full and frank discussion it was decided that the Conference was in complete sympathy with the views expressed by the Pakistan Medical Association, and that it would be the desire of the member nations within the British Commonwealth to do all within their power to meet the needs of a member nation.

4. *Medical Licentiates of India. Request by Dr. A. N. Roy, President of the Bengal Provincial Branch of the All-India Medical Licentiates' Association, that all bans that stand in the way of advancement of this class of medical practitioner from Commonwealth Education institutions be removed.* A communication was received from Dr. Roy requesting that all bans that stand in the way of advancement of members of the All-India Licentiates' Association from Commonwealth Education institutions be removed, as by so doing the goodwill of the largest section of the statutorily qualified medical practitioners of India, who form about 50% of the membership of the Indian Medical Association would be gained.

After a full discussion it was decided to inform Dr. Roy that post-graduate study facilities were a matter for each country concerned, but that his request had been sympathetically considered by the Conference and that it was the opinion of Conference that member countries within the British Commonwealth of Nations were anxious to make available post-graduate study facilities within their areas to other member countries to the degree that this was possible, having regard to the post-graduate requirements of their own students.

5. *Proceedings of the Conference.* It was decided that a statement embodying the proceedings of the Conference should be drawn up, and a copy handed to Delegates to take back with them.

B. *Formal Papers*: The following formal papers were presented to the Conference:—

1. *The Right Honourable Sir Earle Page, G.C.M.G., C.H., M.B., Ch.M., F.R.C.S., F.R.A.C.S., Minister for Health of the Commonwealth of Australia,* delivered an address entitled *A New Conception of a National Health Scheme for Australia.* He stated that his conception was based on a combination of Government aid with nation-wide voluntary insurance against sickness and disease, involving a partnership between the Government and the individual, which is a recognition of the obligations of both the State and the individual in a national health scheme.

The essential factors of a satisfactory solution of a National Health Scheme, and of the necessity of a new approach involving voluntary insurance were dealt with at some length.

The details of the proposed medical benefits scheme, together with the method of its implementation were fully discussed. Figures were given for the costs of existing schemes in Great Britain and New Zealand for comparison with projected costs in Australia.

2. *Dr. H. R. R. Grieve, Member of the Federal Council of the British Medical Association in Australia,* presented a paper on *The Medical Profession's Fight against Socialized Medicine in Australia,* in which he gave a comprehensive account of the different stages of the fight which had been waged by the medical profession in Australia since 1937 against threats of socialization, and discussed the lessons to be learned from the results.

3. *Dr. J. K. Maddox, Past President, British Medical Association, New South Wales Branch,* discussed *Medical Education in Australia,* presenting a historical survey of the development of the four medical schools in Australia, together with an account of the curricula and standards of medical education in Australia and a comparison with those of other countries.

4. *Colonel A. M. McIntosh, President, the Australian Post-Graduate Federation in Medicine, Sydney,* read a paper on *Post-Graduate Medical Education in Australia,* including a survey of its development and a broad account of the facilities now available to local graduates, as well as to visitors from overseas.

5. *Dr. Mervyn Archdall, Editor, The Medical Journal of Australia,* gave an account of *Medical Journalism in Australia,* with special reference to *The Medical Journal of Australia,* of which he is the Editor. He gave a short history of this Journal from the time of its first publication in July 1914, and mentioned the other Journals which are published in Australia. The activities of the Australasian Medical Publishing Company Limited, the Company established by the British Medical Association in Australia for the publication of *The Medical Journal of Australia,* were described.

6. *Dr. C. E. Cook, Commonwealth Health Department (Australia),* discussed *The Problem of Tropical Diseases in Australia, with Special Reference to the Care of the Aboriginal Population.* He presented a detailed account of the historical development of the northern or tropical part of Australia, and its problems in relation to climate and population, and discussed the history of the three main medical problems of the area, i.e. malaria, hookworm and leprosy.

7. *Dr. G. Simpson, Honorary Secretary, Federal Council, Flying Doctor Service of Australia,* read a paper on *The Flying Doctor Service in Australia,* which was regarded as the highlight of the Conference. His historical and factual account of this Service, which is unique in the world, was interspersed with numerous illustrations, a recording of an actual radio consulting session, a sound film of an emergency flight, and demonstrations of the actual wireless equipment used.

Also in attendance were the Very Reverend Dr. John Flynn —'Flynn of the Inland'—who was responsible for the creation of the Service, and Dr. Allan Vickers, the Flying Doctor, now stationed at Charleville, both of whom gave short addresses.

8. *Dr. A. E. Lee, Member of the Federal Council of the British Medical Association in Australia,* gave an account of *The Public Hospital System in Queensland,* in which he told of the replacement of an honorary system of hospital service by a method of staff payments, and the development and implications of a completely free hospital service to every person who desires it.

9. *Prof. Lorimer Dods, Professor of Child Health, The University of Sydney,* discussed an aspect of Child Health in Australia in a paper on *Congenital Malformations following Rubella, and other Noxious Influences during Pregnancy,* which was presented as an account of recent research work in Australia on this important matter. This particular research was initiated by an Australian, Dr. Norman E. Gregg, in the course of a busy medical practice.

10. *Sir John Newman Morris, President of the Medical Board of Victoria,* in a talk on *Medical Registration in Australia,* discussed the various provisions of the Medical Practitioners' Act in the different States.

11. *Dr. A. Macrae, Deputy Secretary of the British Medical Association,* discussed *The Medical Bill, 1950, U.K.,* with its provision for the requirement of post-graduate hospital experience before granting of full registration.

12. *Dr. W. F. Simmons, Member of the Federal Council of the British Medical Association in Australia,* read a paper on the *Organization of the Medical Profession in Australia.* He described the development of the six Branches of the British Medical Association in Australia, and of the Federal Council, the latter body acting for and on behalf of the Branches in matters affecting the profession as a whole, with remarks on the Australasian Medical Congresses and the Government Medical Services. He submitted that the organization of the profession in Australia should be regarded as one unit in the organization of the medical profession of the British Commonwealth of Nations.

A discussion ensued after the reading of each paper.

C. *Social Functions*: During the Conference the Delegates were the guests of the Federal Council of the British Medical Association in Australia to lunch on each of the three days, and to dinner on the final night. Subsequently, all Delegates attended a meeting of the Federal Council and the Australasian Medical Congress, with its accompanying social activities.

D. *Conclusions*: For Australia the session was historic as being the first held in this country.

The most striking impression of the Conference was that of the spontaneous readiness of member nations to unite in strengthening the influence of the British Commonwealth in world affairs. The atmosphere of the Conference was pervaded by the central idea that morally and physically the British Commonwealth was still at once the most compact and the most comprehensive world influence for peace.

The British genius for the rule of the unwritten law was exemplified by the unanimous agreement of the Conference, not however expressed in finite resolutions, that the medical professions of all member nations would come to the assistance of the profession of any member nation adversely affected by civil or martial emergency.

There was evidence and agreement amongst all the Delegates that the value of the results both spiritual and professional of this Conference was increasing.

1 June 1950.

## PASSING EVENTS

### South African Medical and Dental Council—Rules Regarding the Registration of Additional Qualifications

*Government Notice No. 1266 dated 9 June 1950*

The Minister of Health, in exercise of the powers conferred on him by sub-section (4) of section *ninety-four* of the Medical, Dental and Pharmacy Act, 1928 (Act No. 13 of 1928), has approved of the amendment of the rules made by the South African Medical and Dental Council under paragraph (*h*) of sub-section (2) of the said section of the Act and published under Government Notice No. 1371 of 1931, as amended, by the addition under rule (*a*) of the following qualifications:—

Under sub-item (ii) Medicine or Surgery—

| | |
|---|---|
| University of Frankfurt a/Main | Doctor of Medicine. M.D., Univ. Frankfurt a/Main. |

Under sub-item (iv) other—

| | |
|---|---|
| Royal College of Physicians and Surgeons of Ireland | Diploma in Ophthalmic Medicine and Surgery, D.O.M.S., R.C.P.S., Irel. |
| University of London | Diploma in Medical Radiology (diagnosis), D.M.R.D., Univ. Lond. |

### Leukemia Prize

An international competition for the best published paper on acute leukemia and allied conditions is being sponsored by a private foundation in the United States. The Robert Roesler de Villiers Foundation of New York City, named after a gifted boy who died of acute leukemia in 1944, is offering a prize of $500 for the paper which, in the opinion of competent judges, makes a significant contribution to the knowledge and cure of this fatal blood disease.

The judges will be Dr. Albert Adler (Zurich University, Switzerland), Dr. William B. Castle (Harvard University, United States), Dr. Jan Waldenstroem (University of Upsala, Sweden) and Dr. Maxwell M. Wintrobe (University of Utah, United States). The judges are authorized to increase the award to a maximum of $1,000 if they consider the winning paper to be of outstanding importance.

The competition is open to the citizens and residents of all

countries. Papers must be received not later than April 1951. They should have been published or accepted for publication by a reputable journal between January 1950 and 20 October 1951. Contestants living outside the Western Hemisphere are to send their papers to Dr. P. D. Sven Moeschlin, Secretary-General of the Societe Internationale Europeene d'Hematologie, Zurich, Switzerland; those in the Western Hemisphere to Dr. Sol Haborman, Secretary-General of the International Society of Hematology at Dallas, Texas, in the United States.

### MEDICAL PRACTITIONERS AND CURRENCY FACILITIES

An arrangement has recently been made by the Department of Commerce and Industries with Union banks to allow exchange facilities to cover currency required for subscriptions to overseas medical and technical journals and Associations up to a total of £30 per year for any one person.

Medical practitioners should therefore be able to negotiate currency exchange up to this amount without the necessity of an import permit.

### BARAGWANATH MEDICAL SOCIETY

An open meeting, clinical and clinico-pathological, will be held in the Nurses' Training School, Baragwanath Hospital at 8.15 p.m. on 25 July 1950.

* * * *

The marriage of Dr. L. J. A. Loewenthal of Johannesburg to Mrs. Stella Koston, daughter of Mrs. W. Herzfeld of St. James, Cape, took place in Johannesburg on Tuesday, 27 June 1950.

* * * *

When members of Medical Aid Societies require specimens to be examined by the South African Institute for Medical Research, medical practitioners are asked to inform the Institute of the fact that the patient is a member of a Medical Aid Society so that advantage may be taken of the preferential Tariff for Approved Medical Aid Societies.

## NEW PREPARATIONS AND APPLIANCES

### THE GILLETTE RANGE OF SURGICAL BLADES

The Gillette Company has designed a range of surgical blades that combine all the characteristics desired by modern surgery. Not only have the new blades the perfect cutting edges made possible by the use of automatic precision machinery and by rigorous, scientifically devised controls at every stage of production, but their shapes, evolved under professional guidance, fulfil the exacting needs of the surgical profession.

The blade contours, while following the traditional profiles, are so designed as to permit the application of the most modern sharpening methods.

To provide for the various needs of the profession, five different contours have been designed, three for general surgery and two for plastic surgery. All these surgical blades are made from the finest cold-rolled carbon steel, accurately heat-treated to the required degree of hardness and toughness. The process of manufacture is tested at every stage by lynx-eyed devices which detect the most minute defect in the blade, thus ensuring that those passed have a flawless cutting edge, of a sharpness hitherto almost unknown in scalpels or replaceable surgical blades.

Edges of this sharpness are of necessity delicate. The Gillette surgical blades are wrapped in such a way as to protect the edges from mechanical damage or corrosion. Each blade is coated with a protective film and securely anchored in wrappers of waxed paper, which are themselves impregnated with an effective rust inhibitor.

While Gillette surgical blades fit standard handles, it was found advisable, in order to ensure completely accurate fit and rigidity, to produce handles specially made for them. These handles, made from chromium-plated nickel-silver, are precision-machined to the same exacting limits as the blades themselves and form together with them a perfect whole.

Gillette Surgical Blades are kept at the main Provincial Hospitals for the use of surgeons who wish to try them. Surgeons who are unable to obtain the blades are asked to contact the Gillette Safety Razor Company of S.A. (Pty.), Limited (Johannesburg, Durban or Cape Town) who will be happy to arrange supplies.

## REVIEWS OF BOOKS

### BEAUMONT'S APPLIED MEDICINE

*Applied Medicine.* By G. E. Beaumont, M.A., D.M., F.R.C.P., D.P.H. (Pp. 540, with 74 illustrations. 30s.) London: J. & A. Churchill Ltd. 1950.

*Contents:* Part I. Descriptive Cases. Part II. Short Notes on Cases. Part III. Cases Demonstrated at the Bedside by Question and Answer. Part IV. Idle Thoughts.

Dr. Beaumont has become a fairly prolific writer of books for the student of medicine. His latest volume is an interesting departure from the orthodox path which many clinical teachers follow in their more formal writings.

The book is reminiscent of the illustrated case-book which the intelligent student prepares for himself during his clinical rounds. The important principles of diagnostic medicine are illustrated not only with a wealth of clinical description, but also with an extremely well-selected and pertinent set of diagrams, clinical photographs, as well as X-ray films.

The student will find particularly fascinating the section on 'Demonstrations of Cases at the Bedside'.

This is certainly a book no clinical student should be without.

### TUBERCULOSIS

*Tuberculosis in the Commonwealth. The Full Verbatim Transactions of the Second Commonwealth and Empire Health and Tuberculosis Conference,* held in London from 5 to 8 July 1949. (Pp. 411 + viii, with 11 plates. 15s.) London: The National Association for the Prevention of Tuberculosis. 1949.

*Contents:* 1. Photographs. 2. Tuberculosis as a World Problem. 3. Trends in the Modern Treatment of Tuberculosis, including Streptomycin and PAS. 4. Regional, County and County Borough Tuberculosis Schemes. 5. Organization of Comprehensive Tuberculosis Schemes in British Colonies. 6. Problems in the Prevention and Detection of Tuberculosis. 7. Psychological and Social Readaptation of Chronic Disease in Industry. 8. Protection from Bovine Tuberculosis Infection.

These verbatim reports make interesting reading for the Tuberculosis Officer, the Public Health Officer and also for the physician.

The excellent contributions by the Scandinavian delegates on the subject of B.C.G. are especially noteworthy, and many of the papers on trends in the modern treatment of tuberculosis impress the reader by their high academic standard and yet essentially practical approach.

Many of the public health and administrative problems raised are of purely local interest, but it should be stressed that the value of these proceedings was in no small degree due to the presence of delegates from many countries, e.g. Europe, America and Asia, in addition to those from Britain, her Colonies and the Dominions. This converted this Commonwealth Conference for all practical purposes into an International Congress.

The views then expressed and now published are thus a digest of current medical thought on the subject and give an excellent general perspective of tuberculosis as a world problem.

### INFECTIOUS DISEASES

*The Common Infectious Diseases: A Handbook for Students and Postgraduates.* By H. Stanley Banks, M.A., M.D., F.R.C.P., D.P.H. (Pp. 354 + vii, with 90 figures. 21s.) London: Edward Arnold & Co. 1949.

*Contents:* 1. Diphtheria 2. Scarlet Fever and Haemolytic Streptococcal Sore Throat 3. Erysipelas and Erysipeloid. 4. Measles. 5. Rubella and Congenital Malformations. 6. Whooping Cough. 7. Mumps. 8. Glandular Fever. 9. Influenza. 10. Chickenpox. 11. Vaccinia. 12. Smallpox. 13. Meningococcal Fever. 14. Poliomyelitis. 15. Typhoid and Paratyphoid Fevers. 16. Acute Diarrhoea in Infants. 17. Infective Gastro-Enteritis of Infants. Index.

This work by a well-known and highly experienced physician who is Superintendent of a large Fever Hospital is a welcome addition to the literature on infectious diseases.

In the preface the author states that the book is based on lectures given to students and post-graduates, and the reviewer agrees that both these groups will find it of use. For the student it contains much that is useful in his medical course, and for the practitioner it is a handy book of reference. The common infectious diseases are all adequately described, and care has been taken to include modern developments, such as the intensive intravenous antitoxin treatment of hypertoxic diphtheria, the short isolation period of scarlet fever and the abolition of repeated lumbar puncture for drainage in meningococcal meningitis. The frequency and extent of pulmonary collapse in whooping cough is stressed and reproductions of X-ray films are shown to illustrate the condition.

Amongst the 90 figures with which the book is illustrated there are satisfactory monochrome photographs of rashes, though Fig. 84, representing the rose spots of typhoid, gives an exaggerated picture likely to mislead students. In the reviewer's experience rose spots are usually scanty and not so well defined.

## Ocular Disorders and Oligophrenia

*Microphthalmos and Anophthalmos with or without Coincident Oligophrenia: A Clinical and Genetic-Statistical Study.* By Torsten Sjögren and Tage Larsson. (Pp. 103, with illustrations and tables. 15 Swed. Crowns.) Copenhagen: Ejnar Munksgaard. 1949.

*Contents:* 1. Education of the Blind in Sweden. 2. Data concerning the Blind in the official Swedish statistics. 3. Statistic data on the basis of the Registers of the Inspectors of Schools for the Blind and of the Asylum in Lund. 4. Survey of the Literature. 5. The material. 6. Microphthalmos-oligophrenia and isolated microphthalmos as causes of blindness. 7. Distribution according to sex. 8. The mortality. 9. The incidence of microphthalmos-oligophrenia and isolated microphthalmos in the Population. 10. Infant Mortality among the sibs. 11. The age of the mothers. 12. The position of the affected children in the birth series. 13. Microphthalmos-oligophrenia. 14. Isolated microphthalmos. 15. Geographical Distribution. Summary. Conclusions. References.

The authors have made a clinical and genetic study of 137 cases of microphthalmos or anophthalmos with blindness in Sweden; 58 of the cases had associated oligophrenia. Their figures indicate that the coincidence of oligophrenia with microphthalmos and anophthalmos must be a homozygous form of disease or a question of a very strong linkage.

Microphthalmos or anophthalmos without coincident oligophrenia occurs to a certain extent as a dominant hereditary disease. When associated with oligophrenia it occurs as a partially sex-linked mode of inheritance with a reduced degree of manifestation.

This monograph contains a wealth of statistics and tables and one gets the impression that much of this could have been condensed into graphs.

It is not surprising to note, in the preface of this paper, that in progressive Sweden there is a special asylum and institute for blind persons with a complicating disability. Crippleness, blindness and deaf-mutism are notifiable conditions. *All* blind children receive appropriate education and vocational training. Microphthalmos-oligophrenia and isolated microphthalmos are each responsible for 4% of the cases of blindness that reach the age of seven years in Sweden (the incidence of the latter being 0.31 per thousand). The authors found that the average expectation of life is 15-20% lower for a microphthalmos-oligophrenia case than for a person of corresponding age in the normal population. They do not state reasons for this.

Epilepsy was found among 28% of the microphthalmos-oligophrenia cases. Skeletal anomalies were present in 71% of the 45 cases of microphthalmos-oligophrenia.

It would be interesting to follow up the cases of so-called anophthalmos and investigate whether they are true anophthalmos with no trace of an eye primordium on either side, for the true condition is said to be very rare.

This valuable record of a fairly large number of cases of a rare group of conditions will interest ophthalmologists, geneticists, psychiatrists, embryologists and anatomists.

## Murder and the Medico-Legal Pathologist

*The Trials of Frederick Nodder (The Mona Tinsley Case).* Edited by Winifred Duke. (Pp. 242 + xiii. With 10 illustrations. 15s.) London, Edinburgh and Glasgow: William Hodge and Company Limited.

*Contents:* 1. First Trial: First Day—Tuesday, 9 March 1937: Request by the Defence for an Order to be made; Decision by the Court. 2. Second Day—Wednesday, 10 March 1937: Indictment; Opening Speech for the Prosecution. Evidence for the Prosecution. 3. Second Trial: First Day—Monday, 22 November 1937: Indictment; Opening Speech for the Prosecution. Evidence for the Prosecution. 4. Second Day—Tuesday, 23 November 1937: Evidence for the Defence; Further Evidence for the Prosecution. Appendices

This interesting volume in the *Notable British Trials Series* raises several important medico-legal issues. In the first place, the medical reader will find invaluable the data about putrefaction and the development of adipocere in a body immersed in a river for five months. Decomposition was sufficiently advanced to prevent recognition of any coherent structure in the eyes, yet Professor Webster as well as Sir Bernard Spilsbury were quite dogmatic in their view that the post mortem findings definitely excluded drowning as a cause of death. The case was further complicated by the fact that the body of the child was immersed in the river during the cold winter months, a factor which obviously inhibited the putrefactive processes.

In view of the failure of the Defence to challenge these inferences, the interpretation of the autopsy findings in this case deserves very careful consideration and debate by the medical reader.

One of the interesting points commented upon by Professor Webster was that the mucous membrane of the wind pipe was redder in colour than is seen in death from natural causes. 'It was of a redness such as one does see in asphyxial death' (p. 158). This extraordinary statement went unchallenged as well. No doubt Professor Webster meant to convey by his answer that in this body, which had been immersed for five wintry months, he could recognize the mucosal congestion seen in asphyxial death.

Gordon (in the *British Medical Journal*, 1944, **2**, 337) in discussing a classification of deaths of medico-legal importance, has stressed the complete non-specificity of the findings of visceral congestion as evidence of asphyxia. Gordon's views do not appear to be sufficiently well known in Great Britain, as no reference is made to them in the introductory survey prepared by the Editor. The evidence even of so eminent a medico-legal authority as the late Sir Bernard Spilsbury, who confirmed Professor Webster's opinion in this matter, should be re-considered in the light of Gordon's contribution to forensic pathology.

In the case of the particular point under discussion, viz. the unusual redness of the mucous membrane of the wind pipe, there is another very simple observation which could have been the explanation of what Professor Webster saw. It is a common experience of those who dissect dead bodies that, when cadavers have been exposed to considerable cold, the blood undergoes a change in colour to a bright red hue which can even simulate the colour of the blood in acute carbon monoxide poisoning. This would have formed a very sound basis for an attack on Professor Webster's conclusion.

Another point which will interest the medical reader is the attempt to deduce that death was due to a mechanical obstruction to the throat from the finding that the right heart was dilated compared with the left, and that there was no evidence of blood clots in the heart. Gordon's views make it clear that it is dangerous to rely on such non-specific findings when attempting to establish that death was in fact due to a form of anoxic anoxia.

A final point of interest is the opinion expressed by the late Sir Bernard Spilsbury that the body had not risen to the surface until five months later, because of the failure to undergo putrefaction during the winter. In view of the fact that mud was found in the eyes and in the mouth as well as over the surface of the head, the simple explanation of the failure of the body to float may well have been due to the fact that the body was actually stuck in the mud until shortly before it was discovered. This explanation was, however, not thought of by the defending Counsel, and it seems a great pity that such very simple alternative explanations were not explored.

From these few points which have been raised for discussion, it is clear that the *Trials of Frederick Nodder* is virtually an important textbook for the student of medical jurisprudence and as such the volume deserves the most serious and careful study by all medical practitioners.

The reader will, however, find also much enjoyment in the astute and incisive observations as well as the telling comments and retorts by way of repartee which were indulged in by Mr. Justice Swift in the first of Frederick Nodder's trials. His tussles with the expert witnesses and his verbal wrestling with Counsel make this verbatim record a very entertaining as well as a very instructive one.

### BUCHANAN'S MANUAL OF ANATOMY

*Buchanan's Manual of Anatomy.* Edited by F. Wood Jones, D.Sc. (Lond., Adelaide and Melb.), M.Sc. (Manch.), M.B., B.S. (Lond.), F.R.S., F.R.C.S. (Eng.), F.R.A.C.S. (Pp. 1616 + viii, with 847 figures. 45s. Eighth edition.) London: Baillière, Tindall & Cox. 1949.

*Contents*: 1. Terminology and Relative Positions. 2. The Development and Growth of the Human Body. 3. Osteology. 4. The Bones of the Trunk. 5. The Bones of the Head. 6. The Bones of the Upper Limb. 7. The Bones of the Lower Limb. 8. The Upper Limb. 9. The Lower Limb. 10. The Abdomen. 11. The Thorax. 12. The Head and the Neck. 13. The Nervous System. 14. The Eye. 15. The Ear. Glossary. Biographical Notes. Index.

This is definitely becoming one of the most accurate and complete textbooks of gross topographical anatomy.

The chapter on the development and growth of the body has been summarized to a bare minimum. In view of the increasing number of books devoted solely to embryology, this is a justifiable procedure.

The editor's appreciation of the growing need to teach 'normal' X-ray appearances to the medical student is indicated by the large number of beautifully clear skiagrams. Markers indicating the more salient features would enhance their value.

The diagrams are all of the black and white line, and shading type, and despite the statement in the preface that coloured figures are '. . . unnecessary and, at times, misleading', the reviewer feels that colour, if used only to delineate vessels and nerves in complex diagrams, is of great assistance to visual memory. One realizes, of course, that coloured plates greatly increase the cost of a book. In many of the diagrams, however, heavy shading obscures detail and even the pointers. In the osteology sketches one does not appreciate the 'smoothness', 'roughness', 'pits', 'prominences', 'ridges', etc., of the bones, which are so essential to their understanding.

The section on the abdomen commences with a detailed description of the perineum, whereafter the wall and contents of the abdomen proper and pelvis are described. This order of instruction or study is different from that in most textbooks and has no apparent advantage. Since the abdominal fasciae are extended into the perineum, and the blood and nerve supply are continuous with vessels and nerves in the abdomen, it would appear logical to describe the abdomen proper primarily.

The clarity of description and the wealth of detail make this an excellent textbook for under- and post-graduate students, and an essential for an anatomist's reference library.

### DIE SPYSVERTERINGSKANAAL EN TUBERKULOSE

*Röntgenonderzoek bij Darmtuberculose.* Deur T. J. J. H. Meuwissen. (Bl. 243, met 103 illustrasies. F. 25.) Leiden: H. E. Stenfert Kroese's Uitgeversmij. N.V. 1949.

*Inhoud*: 1. Klinische Verschijnselen. 2. Pathologische Anatomie. 3. Verschijnselen bij Röntgenonderzoek. 4. Overzicht der Gevallen. 5. Besluit.

Hierdie kort maar doeltreffende monografie van werk tussen 1937 en 1942 is baseer op die ondersoek van die ileo-caecal streek en die colon deur middel van die barium klisma metode in gevalle van long-tuberkulose.

Die voorstelling is kort en duidelik. Die illustrasies, deur X-straalfotos en verklarende buitelyntekeninge, is uitstekend. In die inleiding word daar hulde aan hulle betoon wat die waarde van die slymvlies patroon plate in die X-straal-diagnose van die spysverteringskanaal ontdek het, i.e., Berg, Knothe, Albrecht, Forsell, Stierlin, en in Holland, Bronkhorst.

'n Kort opsomming word in die eerste hoofstuk gegee van die kliniese voorkoms, en daar word besonder nadruk gelê op die feit dat wanneer die longontsteking bevredigend is, maar die pasiënt agteruitgaan, X-straal-ondersoek van die spysverteringskanaal nie nagelaat mag word nie.

Hoofstuk 2 gee 'n oorsig oor patologie wat hoofsaaklik op die werk van Sampson en Brown van Saranac Meer, V.S.A., baseer is. Die aantal gevalle van spysvertering-tuberkulose in long-tuberkulose wissel naastenby van 30-38%, deur X-straal-ondersoek ontdek. Deel een, van hoofstuk 3, gee 'n beskrywing van die X-straal-ondersoekmetode waarin die gewone barium-maal en barium klisma toegepas word. Dit is merkwaardig dat die kleinderm klisma, as 'n metode van ondersoek, uitgelaat is.

Direkte en indirekte X-straal verskynsels met gevalle wat ,verandering van die caecum, verkorting van die colon ascendens, uitsparring van die caecum, swelling van die valvula Bauhini, verandering in die slymvlies van die caecum en ileum' illustreer, word in die tweede helfte van die hoofstuk behandel. Die demonstrasie van die swelling van die valvula Bauhini is besonder interessant. Gevalle word in die vierde hoofstuk hersien deur 'n kort kliniese samevatting wat gepaard gaan met X-straalfotos.

Die skrywer se gevolgtrekking is dat elke geval van Koch se siekte 'n X-straal-ondersoek van die spysverteringskanaal behoort te hê. Aan die einde van die boek is daar 'n kort oorsig.

Die kwaliteit papier en die drukwerk dra daartoe by om die boek se waarde te verhoog.

### YEAR-BOOK OF OBSTETRICS AND GYNECOLOGY: 1949

*The* 1949 *Year-Book of Obstetrics and Gynecology* (*October* 1948-*August* 1949). Edited by J. P. Greenhill. (Pp. 629, with 132 illustrations. §4.50.) Chicago: The Year-Book Publishers, Inc. 1950.

*Contents*: I. Obstetrics: Pregnancy: 1. Physiology. 2. Abortion. 3. Ectopic Pregnancy. 4. Complications. 5. Toxemia. 6. Labor: General. 7. Anesthesia. 8. Complications. 9. Operative Obstetrics. 10. Uterine Hemorrhage. 11. Puerperium. 12. The Newborn. II Gynecology 13. General Principles. 14. Diagnosis. 15 Infertility. 16. Operative Technic. 17. Infections. 18. Benign Tumors. 19. Special Ovarian Tumors. 20. Malignant Tumors. 21. Menstruation. 22. Endocrinology.

This edition of an already well-known book in academic obstetrics and gynaecology will be welcomed by all those interested in the latest advances in this field.

It is difficult to appraise adequately a book which is itself a digest of the year's obstetrical and gynaecological literature, not to mention valuable information on the newborn child.

Like previous volumes, this edition deserves nothing but praise for the editor's choice of material for inclusion.

Professor Greenhill has surely captured the imagination of all his readers by his excellent and concise criticisms, more of which would be welcomed from such an eminent authority.

Not only are the abstracts well chosen, but due emphasis is laid on original works, with an excellent index of the subject matter and authors' names.

The dust wrapper again contains the customary 'quiz'. We must confess to being unable to answer the majority of questions without referring to the contents of the book.

Of interest among the hundreds of articles summarized, one notes the warning on the cautious use of morphine in eclampsia, owing to the risk of urinary suppression. Crede's method of expression of the placenta is again condemned, manual removal in the hands of the expert being considered less risky. A word of warning is noted in the use of pituitrin for postpartum haemorrhage where manual removal is contemplated under cyclopropane or pentothal anaesthesia, because of the danger of sudden death.

Among gynaecological articles, H. S. Taylor's contribution on vascular congestion and hyperaemia should be closely studied.

Obstetricians and gynaecologists will surely add this interesting book of the year to their previous editions.

### GLOSSOPHARYNGEAL NEURALGIAS

*Névralgies du Glosso-Pharyngien.* By Maurice Deparis. (Pp. 156, with 5 figures. 360 francs.) Paris: Masson et Cie. 1949.

This book gives a systematized account of the fortunately somewhat rare glossopharyngeal neuralgias. It is richly documented with references not only to the cases and views of French neurologists, but to all that has been written and done for this shockingly painful condition by British and American physicians and surgeons.

True to the French tradition in neurology, it commences with lucid accounts of the complex anatomy and physiology of the glossopharyngeal nerve and its important connections with the facial, the vagus and the sympathetic. This (ninth cranial) nerve supplies the soft palate, tonsils and the posterior third of the tongue, together with the naso- and oro-pharynx. It is interesting to note that French anatomists credit this nerve with, amongst other muscles of the throat and palate, the motor nerve supply of the styloglossus muscle, whereas most English textbooks assign this last function dogmatically to the hypoglossal nerve. It is refreshing also to find that the tiny anatomical 'curiosity', the tympanic branch (Jacobson's nerve), can be the basis of a purely tympanic type of neuralgia (Reichert).

Thjs anatomical background explains the point of departure of the paroxysmal pain from a very limited zone of one side of the throat, the tonsillar fossa or back of the tongue to its ultimate radiations.

The specially excruciating nature of this pain with its 'trigger zones', refractory states and remissions are all suitably discussed and compared with the corresponding phenomena of trigeminal neuralgia; but the author does not claim more than to try to throw some additional light on the mysterious quantity that 'tic douloureaux' still remains.

Clinically the disease is classified into the usual primary or idiopathic types; secondary or symptomatic resulting from tumours or from simple pressure, such as from an enlarged styloid process; and he refers to a third type which has a subjective neurotic basis. Curiously enough, suicide is most commonly resorted to for relief by the last group.

With true Latin logic the author quotes the experience of those who claim successes with the usual hypno-analgesic medicines, and recommends their trial. It would appear, however, that the majority of cases sooner or later requires some form of injection and ultimately even radical surgical intervention.

The indications, techniques, successes and failures of these procedures are all duly set out in interesting chapters of this exhaustive treatise on the vilest of human tortures.

### WILLIAM WITHERING

*William Withering of Birmingham, M.D., F.R.S., F.L.S.* By T. Whitmore Peck, M.P.S., and K. Douglas Wilkinson, *O.B.E.*, M.D. (Birm.), F.R.C.P. (Lond.). (Pp. 239 + viii. With 52 plates. 21s.) London: John Wright & Sons, Limited.

*Contents*: 1. Introductions. 2. Beginnings. 3. Training. 4. The Young Physician. 5. An Account of the Foxglove. 6. The General Hospital. 7. Medical Practice. 8. Interests. 9. Property. 10. The Riots of 1791. 11. Tuberculosis.

The increasing number of practitioners interested in the history of medicine will welcome this extremely thorough and well documented account of Dr. William Withering, whose 'An Account of the Fox Glove and Some of its Medical Uses: with Practical Remarks on Dropsy and Other Diseases' was published by Dr. Withering when he was physician to the General Hospital at Birmingham.

It is an extraordinary matter for reflection that Withering's account of the fox glove has endured in respect of accuracy and usefulness for the whole period of the 170 years since it was first written. It must still be regarded as one of the really great English contributions to therapy.

He first put pen to paper about 10 years after he had begun to use these medicines, and in making his report he was careful to include all cases treated, whether successful or otherwise.

A considerable proportion of the book is taken up with the disputations and controversies in which Withering found himself involved in espousing the use of digitalis. Copies of the polemics, including the letters from Dr. Darwin written with characteristic vituperation, are included in full, and these add to the lively account which the authors have prepared. The book will be enjoyed by all who are concerned with practice of pharmacy or medicine.

## CORRESPONDENCE

### WORLD HEALTH ORGANIZATION

*To the Editor*: The work of the World Health Organization deserves to be better known among the people of South Africa. This Organization, which may be aptly described as the natural child of universal human suffering, came into formal existence with the ratification of its provisional Constitution by 17 nations on 29 September 1947. The World Health Organization has very properly taken over the technical functions of the U.N.R.R.A., the Health Organization of the League of Nations, and the Office International d'Hygiene Publique. The 12th Pan-American Sanitary Organization has generously agreed to constitute itself as the Regional Office of the W.H.O. in the Western Hemisphere in accordance with the constitution of the W.H.O. and the terms of an appended agreement. This change took place with the approbation of the agreement by the W.H.O. and 14 of the American Republics.

The W.H.O., although in existence for only two years, has already established a fine record of constructive activity. Its more outstanding achievements in the field of international well-being include the following:—

1. The selection and maintenance of a large number of students from various countries for post-graduate training in public health, medicine, sanitation, and nursing;
2. The provision of medical literature for Yugoslavia and other countries;
3. The maintenance of missions of technical experts in China, Greece, Italy and other countries to assist the public health authorities and to train native personnel;
4. The assignment of a Committee of six to the Middle East to study health problems which are particularly incidental to the pilgrimages to Mecca, and to make recommendations in connexion therewith for the consideration of W.H.O.;
5. The transmission of seven tons of medical supplies and vaccines to the Egyptian Health Ministry to combat the cholera epidemic which resulted in more than 2,000 deaths;
6. The appointment of 10 technical committees to study the problem of malaria, venereal diseases, and the standardization of biological products, and also to prepare a revision of the International List of Diseases and Causes of Death;
7. The formulation of plans for the First World Health Assembly held in the U.S.A. in 1948;
8. The utilization of 12 radio stations in the Far East for the relay of epidemiological and technical information to public health and maritime personnel in that part of the world;
9. The initiation of a programme for the publication of technical journals;
10. The initiation of negotiations with the International Labour Organization (I.L.O.), United Nations Educational, Scientific, and Cultural Organization (U.N.E.S.C.O.), International Food and Agriculture Organization (I.F.A.O.), International Children's Emergency Fund, and International Civil Aeronautical Organization (I.C.A.O.), with a view to the organization of a co-ordinated attack on mutual problems, and the elimination of overlapping.

Special reference is indicated in respect of the work of the International Children's Emergency Fund which was brought into being by W.H.O. for the express purpose of rendering aid to the stricken children of war-torn Europe. By virtue of this Fund, it was made possible to supply one pint of milk to more than 5,000,000 children in Europe and China. High praise is due to the U.S.A. in this connection in that she contributed $15,000,000 of the $20,000,000 collected from all interested countries.

It deserves to be put on record that the Government of the Union of South Africa has done more than its share in contributing to the success of W.H.O., and that through the

distinguished experts it has sent abroad, it has maintained its good name, and high standing among the nations of the world. The Union Government has always played a prominent part in international health work. Thus it sponsored two important Pan-African League of Nations Health Conferences in 1932 and 1935; and it was represented at the International Health Conference in New York in 1946. At the two assemblies South Africa made an important contribution to the discussions, and on being unanimously elected to the Executive Board, she was able to participate effectively in formulating the policy of the World Health Organization. It is easy to visualize that in the not too distant future South Africa will be called upon to play a more direct part in the promotion of world health, and this will undoubtedly happen when the African Region of the World Health Organization is established for the purpose of serving that portion of Africa south of the Sahara. Within the framework of the W.H.O. regional organization, South Africa, by virtue of her own great national health services, and her progressive universities and medical research institutions, will be able to make a major contribution to health and medical progress in this Continent. This vision of what is to be is amply sustained by the White Paper presented by the Union Government before the third session of the World Health Organization which opened in Geneva on 8 May 1950.

Louis F. Freed.

2 Barbican Buildings,
President Street,
Johannesburg.
6 June 1950.

## MEDICAL FILMS

*To the Editor*: The U.S. Information Service Film Library has recently received one print each of the medical films listed below,* and believes that your Association and its members might be interested in viewing them, according to their special fields. All of the films listed are 16 mm. silent and sound. They are available only until 1 November, having been obtained on loan. Associations, institutions, and individuals interested in screening any of the listed films, may obtain them by calling or writing to this office.

In addition to the films listed herewith, the Library has more than 150 films on general subjects—agriculture, geography, science, etc. Institutions and organizations interested may obtain catalogues from this office.

Ben A. Thirkield,
*Information Officer.*

U.S. Information Service,
23 Beckett's Buildings,
President Street,
Johannesburg.
7 June 1950.

* Fractures: An Introduction (Sound).
Skin Antiseptics (Sound).
The Physiology of Normal Menstruation (Sound).
The Rehabilitation of Laryngectomized Patients (Sound).
Supradiaphragmatic Vagotomy for Peptic Ulcer: The Abdominal Approach (Silent).
Topical Flourides: Technique of Application (Sound).
Safer Gastrectomy (Sound).
Diseases of the Gall Bladder (Silent).
Perforated Ulcer (Silent).
Kidney Function in Health (Sound).
Energy Release From Food (Sound).
Laboratory Diagnosis of Tuberculosis: Preparation of a Culture Medium (Sound).
Laboratory Diagnosis of Tuberculosis: Preparation of a Sputum Specimen (Sound).

## THYROID TREATMENT OF HYPERTENSION

*To the Editor*: I would be grateful if you would give me the opportunity to reply through your columns to the many enquiries I have had about the preparation of thyroid to use in the treatment of essential hypertension and also to answer the points raised in the letters of criticism which have appeared.

The preparation is, of course, Thyroid Ext. Sicc. as laid down in both the British and United States Pharmacopiae. It is required by both that the preparation be assayed for iodine content (U.S.P. twice strength of B.P.) but as it has been shown that the iodine content may have little or no relationship to pharmacological activity, one should only use preparations which, in addition, have been bio-assayed. There are several such on the market. The recently synthesized L-Thyroxine Sodium offers a hope that our difficulties with inactive or varyingly-active thyroid extracts are at an end.

Coming now to the letters of criticism, I note that Dr. Gilroy is worried about diagnostic standards. How is the diagnosis of essential hypertension made? As it is a clinical diagnosis, it is based on the facts obtained by the use of the clinical method, i.e. on facts obtained from the symptomatology, the past history, the family history and the physical signs. However, in a certain number of cases the raised blood pressure is the only abnormality found, just as in certain cases of diabetes the only abnormality is the presence of sugar in the urine. In such a case, the fact of hypertension having been established by readings taken over a period, the diagnosis is made by a process of exclusion. If no renal factor is demonstrated, if coarctation of the aorta and certain rare endocrine disorders can be excluded, then on the balance of probability the case is one of essential hypertension, for this is far the commonest 'kind' of hypertension. In 100 cases, I would say that 15 would be renal in origin, one to five would be due to other (rarer) causes and 80-85 would fall into the group labelled 'essential'. In this context I cannot help feeling that Dr. Gilroy betrays a tendency to underrate the importance of the subjective aspects of the problem. May I say that the diagnostic difficulties of the clinician who eschews symptomatology will not be limited to essential hypertension.

In discussing the problem of diagnosis Dr. Gilroy makes the astonishing statement that 'most authorities are agreed that in order to diagnose simple or essential hypertension evidence of cardiovascular hypertrophy (i.e. medial hypertrophy of the arteries and left ventricular hypertrophy) must be found in addition to the high blood pressure'. With this statement I find myself in complete disagreement. There must be very few 'authorities' left who would take up such an untenable position. I would say that to-day 'most authorities are agreed' that essential hypertension is a psychosomatic disorder characterized at first by a 'functional' rise in blood pressure due to vasoconstriction and that only in its later stages—years after its onset—is it attended by 'medial hypertrophy of the arteries and left ventricular hypertrophy'. Fishberg (1939) says: 'The conception that hypertension is produced by functional vasoconstriction has steadily gained ground and is now almost universally accepted.'

Both your correspondents rush in to inform me that the blood pressure may be subject to great variations, that the reading obtained will depend on where and how it is taken. As a clinician of 24 years' standing I feel that I have a right to resent this. This knowledge is as old as the sphygmomanometer itself; and while I am on this matter of resentment I think that I also have a right to feel a little hurt by Dr. Segal's comment: 'No mention,' he says, 'is made of any adjuvant treatment, e.g. sedatives, diet, etc.' Is he serious? Does he really believe that anybody making a therapeutic trial of a substance would willingly add to his troubles by resorting to 'shot-gun' methods?

The very fact of the variability of the blood pressure makes the rigid control, which your correspondents and other critics demand, impossible of attainment. 'Control' methods in the solution of clinical problems have a very limited range of usefulness. In this particular problem, proof of the efficacy of thyroid therapy will come from an accumulation of evidence, from clinical experiments conducted by other clinicians. They and their patients will decide the issue.

May I be allowed to digress here and make the suggestion that in experiments devised to test the therapeutic efficacy of any preparation, surely it is the clinician's experience which provides the 'control'? For example, I am familiar with the clinical picture and the course of typhoid fever because I have treated a great many cases. I try out the effects of a new medicament and find that after using it, an illness which I expected to last for weeks clears up in as many days. I repeat the trial several times and obtain the same result. Surely I am justified in claiming in the light of past events

that the new treatment is effective? Would you then have me divide the next 100 cases into two groups treating one and not the other? I may be squeamish, but I would consider such a procedure, to say the least of it, unjustifiable.

Reverting to Dr. Gilroy's difficulties, we come to this enquiry about the treatment of a case of occult hyperthroidism with hypertension. In the rare instances where a systolic hypertension is found in masked or occult hyperthroidism, Dr. Gilroy would find a disproportionately low diastolic pressure. This, in association with other signs and symptoms, would enable him to make a diagnosis. Naturally he would then treat such a case, not with thyroid but with thiouracil.

Let me now deal with the thyrophobia which, in spite of the evidence adduced in my paper, still obsesses my critics. I would like to state at once that nothing has accrued in the six months since I read my paper to cause me to change my mind about the harmlessness of thyroid extract. With the one exception mentioned, namely, angina of effort, I have found that the administration of thyroid extract, in doses which the patient will tolerate, is perfectly harmless. One of the first patients to be given thyroid, an elderly woman aged 75, has been taking 2 to 3 grains daily for 18 months. Another, with an enlarged heart, pulsus alternans, numerous attacks of paroxysmal nocturnal dyspnoea and one episode when he was admitted to hospital with right-sided congestive failure, has been on doses between gr. 5 and gr. 10 for the past three months. His pulse rate has come down from 120 to 72 beats per minute, his blood pressure from 270/160 to 220/130 mm. Hg and his pulsus alternans has disappeared.

I would like to state here that marked lowering of the diastolic pressure (with the audibility of the pulse at the elbow) down to very low levels, no longer occurs now that I am using smaller doses. I have therefore concluded that this is a sign of overdosage.

Dr. Gilroy states that thyroid extract increases the output of the heart. This occurs, for instance, in the treatment of myxoedema where, as a result of thyroid medication, the pulse rate becomes more rapid and the peripheral flow increased. Is this harmful? In a case of essential hypertension where the left ventricle is contracting against considerable resistance, would a lowering of this resistance not ease the burden on the heart? In hyperthyroidism there is no doubt that vasodilatation increases the work of the heart and may lead to left ventricular failure. It is conceivable that, if one persisted with large doses for long periods (always assuming that the patient would continue to take his medicine) cardiac failure might also occur as a result of thyroid administration.

But the object of treatment is *not* to give large doses and cause the symptoms and signs of overdosage. It is directed at finding just that amount of thyroid extract which, when administered, gives rise to no untoward symptoms whatever. In treating diabetes one does not give insulin in order to cause a hypoglycaemic attack. The patient placed on the correctly determined maintenance dose will thus have no palpitation, no asthenia, no choking sensation in the neck, no dyspnoea, no excessive sweating, no tremor, no increased metabolic rate, no raised pulse pressure, no tachycardia. The possibility of a tachycardia causing a fall in blood pressure and cardiac failure, the point raised by Dr. Segal, thus does not arise.

Finally I would like to draw the attention of your correspondents to work done on the correlation of thyroid function and arteriosclerosis (Kirk, Chieffi and Kountz, July 1949, *Journal of Gerontology*, **4**, 185-272). These investigators found that there was a tendency for low blood iodine values and a reduced metabolic rate to be associated with calcification of the popliteal and intermetatarsal arteries and with an increased diameter of the aortic shadow. It is not at all unlikely that a similar correlation will be found to exist between a reduced metabolic rate and essential hypertension. All that we are doing, then, by giving thyroid to cases of essential hypertension is redressing a balance which has been disturbed in the opposite direction by thyroid insufficiency.

Pericles Menof.

607 Medical Centre,
Jeppe Street,
Johannesburg.
8 June 1950.

## PART-TIME POSTS IN HOSPITALS

*To the Editor*: The complaint that certain incumbents of part-time posts in the Transvaal Provincial hospitals are not fulfilling their contracts, is not so much concerned with the number of hours put in, as with the number of sessions.

Obviously, if a man finishes his work conscientiously in less time than is called for per session, then there is no sense in his hanging round. But if he does not put in the number of sessions called for in his contract, that, to my mind, is a breach of faith.

Dr. Lewis Robertson writes that the Superintendent of the General Hospital, Johannesburg, stated to the *Star* that his 'attention had not been *drawn*' to any such occurrence. That is no proof that such action is not taking place. No doctor will report a colleague, but he can ventilate the matter in his own *Journal*.

Dr. Robertson objects to this, as the lay press publish matter from our *Journal*. This applies to Dr. Robertson's letter too, but that does not deter him from writing a letter which implies that the medical profession here contains a man so low that he will write a letter averring facts which are not true. With what object?

There are eight hospitals on the Reef staffed by part-time specialists from Johannesburg. It takes an hour by motor car to reach some of them. Certain specialists from Johannesburg took on positions at these Reef Hospitals when they knew before they applied, that they would not be able to devote the time for the *sessions* in their contracts. Now that they have been appointed they are not putting in the number of *sessions* they contracted to do, and are thus not only laying us open to a strong attacking weapon, but they kept other people out of these appointments, as the letter by '*Done out of a Job*' proves, and which should satisfy Dr. Robertson that the facts are as stated.

If members of our profession do not want to give the lay press an opportunity of publishing facts which reflect on the profession, then their conduct should be like 'Caesar's wife'.

'*Equity*.'

15 June 1950.

## WIND SCREEN DIPLOPIA

*To the Editor*: I wish to record what might be termed 'Wind Screen Diplopia', of which I have had three cases during the past five months.

The patients complained that the lights of oncoming cars became doubled, the second pair of lights being above and slightly to one or the other side of the true light. This diplopia plus a certain amount of dazzle produced a panic and the patients were afraid to drive at night. All noted that when they looked away from the lights other objects were not doubled.

No doubt many others have noted the second image but have realized it is merely an optical phenomenon and not the fault of the eyes. However, the sudden doubling of oncoming lights of a car speeding out of a black background can quite easily be understood to initiate a start reaction, especially in the neurotic and in those with a complex about their eyes, e.g. some high myopes.

The second image is always much dimmer than the true light. It is caused by an internal reflection within the oblique thick glass of some of the rays coming from the light. The obliquity of the glass is the important factor, but I have noted that in the new models of cars many wind screens have a curvature in the glass as well which intensifies this internal reflection and separates the images even more.

The three cases I saw have all occurred in cars with the curved type of wind screen.

A hooded light of moderate intensity shows this doubling best, e.g. robot lights.

E. Epstein.

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